THE YEAR BOOK *of* MEDICINE

(1955 1956 YEAR BOOK *Series)*

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THE PRACTICAL MEDICINE YEAR BOOKS

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DEPARTMENTS *of the* YEAR BOOK *of* MEDICINE

Infections

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The articles abstracted herein are taken from journals received between May 1954 and May 1955

PART I

PART II

THE CHEST

PART III

THE BLOOD AND BLOOD FORMING ORGANS

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

INFECTIONS

PAUL B BEESON M D

PART I

INFECTIONS

IMMUNITY AND INFECTION

Properdin System and Immunity I Demonstration and Isolation of a New Serum Protein Properdin, and Its Role in Immune Phenomena Immunity may be divided into two general classes acquired (artificial) and innate (natural) The discovery of antibodies in serum has increased knowledge of the mechanism of acquired immunity but little is known about the factors involved in natural immunity

In an attempt to isolate one of the components of complement Louis Pillemer Livia Blum Irwin H Lepow Oscar A Ross Earl W Todd and Alastair C Wardlaw[1] (Western Reserve Univ) encountered a new serum protein. Tentatively named properdin it acts only in conjunction with complement and Mg^{++} and participates in such diverse activities as destruction of bacteria neutralization of viruses and lysis of certain red cells It differs from antibody in many respects particularly in its lack of specificity and in its exact requirements for its interactions

Human properdin is a euglobulin with a molecular weight at least eight times that of gamma globulin It represents not more than 0 03% of the total serum proteins Of the warm blooded animals tested the rat has the highest titer of properdin the guinea pig the lowest while that of man is intermediate These findings suggest that properdin may be important in natural immunity for the rat is very resistant to infection the guinea pig quite susceptible

In experiments on bactericidal activity of human serums the authors used Shigella dysenteriae All normal human serums were highly bactericidal Serum from which properdin had been completely removed (RP) was nonbactericidal as was properdin by itself RP was bactericidal when sufficient properdin was again added to give the concentration

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(1) S 120 279 285 A g 0 1954

monic consolidation In June 1952 she had acute meningitis and spinal fluid culture disclosed Hemophilus influenzae Between November 1952 and April 1953 she had repeated attacks of otitis media pharyngitis and pneumonitis During hospitalization in April total serum protein of 3 8 Gm /100 cc with globulin of 1 06 Gm led to the first suspicion of the syndrome of low gamma globulin

Her blood was type B Rh positive of subtype Rh_1 probably homozygous Anti A isoagglutinin titers in saline solution were all negative Electrophoretic analysis of serum three weeks after injection of gamma globulin showed no gamma globulin peak Quantitative immunochemical determination of gamma globulin showed 25 mg /100 cc approximately 0 5% of plasma proteins (normal 14%) After discharge she received 30 cc purified gamma globulin (0 1 Gm /kg body weight) each month Subjective improvement was apparent 48 hours after the first injection No acute infections developed thereafter chronic cough became less productive both tympanic membranes appeared normal and chronic tenosynovitis cleared

Replacement of gamma globulin requires approximately 0 1 Gm /kg to reach blood levels adequate to control infection (100 150 mg /100 cc) Lower levels are of little value In children this dose must be given every four to six weeks in adults whose gamma globulin half life may be less treatment may be needed more often Complexity of electrophoretic or immunochemical study of plasma proteins limits their use to the research laboratory but suspected cases may be screened by determination of isohemagglutinin titers persons with a measurable titer do not have an absence of gamma globulin In the absence of isoagglutinins the suspected diagnosis may be confirmed by quantitative determination of gamma globulin Absence of gamma globulins should be suspected in adults as well as children with multiple respiratory and other infections and perhaps in spruelike syndromes Since the defect can apparently be corrected by replacement therapy which limits disability and forestalls further complications from infections diagnosis is of considerable importance

[The technic of filter paper electrophoresis is becoming available in many hospitals now and because of that we will be able to test frequently for absence of gamma globulins The condition is probably not too rare —Ed]

Adult Agammaglobulinemia Since Bruton in 1952 reported a case in a boy of recurrent bacterial infection with no gamma globulin and an otherwise relatively normal plasma protein pattern similar cases have been reported in male

present in normal serum indicating that properdin, acting with factors present in RP was involved in the bactericidal activity of normal serum against the dysentery bacillus

Severe bacteremia is common following total body irradiation of animals Experiments to test the possibility that the properdin system might be destroyed by total body irradiation revealed that properdin falls conspicuously during the early postirradiation period Low properdin levels reached two to seven days after irradiation suggest a causal relation between the destruction of properdin and onset of severe fatal bacteremia

Investigation of the role of the properdin system in the heat labile antiviral activity of human serum revealed that properdin and serum factors resembling or identical with components of complement are necessary for inhibition of viral hemagglutination Inactivation or removal of any of these factors inhibits antiviral activity Addition of human properdin to serum deficient in properdin restores its antiviral activity

[The discovery of properdin (pro pear -din) appears to be a major event in immunology We are going to hear much more of this in the next few years —Ed]

Absence of Serum Gamma Globulins in an Adult is reported for the first time by Jay P Sanford Cutting B Favour and Melvin S Tribeman[2] (Harvard Med School) The first case of agammaglobulinemia was reported by Bruton in 1952 in a boy 8 who had had 16 bouts of sepsis with eight different pneumococci 5 episodes of otitis media and 3 attacks of epidemic parotitis Deficiency in serum gamma globulin was demonstrated and recurrent infections were controlled by repeated injections of gamma globulin Nine other male children with this syndrome have since been described

Woman 39 on hospitalization in 1953 had had frequent colds with bronchitis since early childhood and a chronic cough had been present since age 17 At 23 anorexia weakness weight loss and watery diarrhea led to an ischiorectal abscess requiring surgery In 1947 three upper respiratory infections were treated with penicillin and bilateral otitis with a sulfonamide After hospitalization in 1948 and treatment by postural drainage vitamins diet and aerosol penicillin she did reasonably well until February 1951 when myringotomy was performed for acute otitis media complicated by pneu

(2) New England J Med 250 1027 1029 June 17 1954

Univ) describe in detail a method for preparation of suspensions of killed T pallidum that are suitable for specific agglutination studies and can be stored at 4 C for months without loss of agglutinability The suspensions were shown to react with two distinct antibodies in the serum of syphilitic animals and man Wassermann antibody and a specific treponeme agglutinin The agglutination of treponemes by specific agglutinin is enhanced by heat treatment or aging of the suspension and inhibited by a divalent cation probably Ca^{++} normally present in serum The inhibition was overcome by use of a chelating agent With these findings the authors devised a simple agglutination test for diagnosis of treponeme infections The test was carried out with 430 human serums Comparison of results with those of the immobilization test showed that the agglutination reaction is a very sensitive test for treponeme antibodies and that its specificity compares favorably with that of the immobilization test Despite the necessity to absorb serums for removal of Wassermann antibody the test is simple and can be made under conditions in which the immobilization test cannot The specificity of the agglutination test was much greater than that of the standard serologic tests

Final evaluation of the agglutination test must come from the critical analysis of results obtained with serums from a large number of patients who have been subject to the most searching clinical and epidemiologic study

[The description sounds as if a really practical specific test for syphilis has been devised It is a pity that something of this kind was not available a few years ago when the disease was a major problem in this country Undoubtedly many persons who did not have syphilis were given that diagnosis and treated for it on the basis of the standard serologic tests —Ed]

STUDIES OF ANTIBIOTIC ACTION

Mechanism of Action of Penicillin Our understanding of this as Harry Eagle[5] (Nat l Inst of Health) reminds us lags far behind its practical application in treatment Penicillin is only one of numerous drugs of unparalleled activity which have been discovered independently of studies of cell

(5) J l La cet 75 1 6 J y 1955

children Robert L Wall and Samuel Saslaw[3] (Ohio State Univ) report this syndrome in two adults

CASE 1 —Man 26 hospitalized for a third attack of pneumonia in a year had also had recurrent erysipelas of the face The sputum contained predominantly beta hemolytic streptococci and staphylococci With penicillin and streptomycin therapy he became afebrile on the third day Electrophoretic studies of plasma showed no gamma globulin He did not form antibodies in response to inoculations with triple typhoid influenza and mumps vaccines In the next few months he had two respiratory infections

CASE 2 —Man 40 was first seen because of fatigue diarrhea nasopharyngitis and minimal lymphadenopathy The site of a lymph node biopsy (which showed reticulum cell hyperplasia) failed to heal for 2½ months despite vigorous antibiotic therapy In the next two years he had repeated infections including a furuncle upper respiratory infection with purulent conjunctivitis bronchitis and repeated bouts of diarrhea Electrophoretic analysis showed lack of gamma globulin The blood was type A and lacked anti B isoagglutinins Subsequent infections included three attacks of left basilar bronchopneumonia maxillary sinusitis and bronchitis and a recurrence of diarrhea After immunization with typhoid paratyphoid vaccine there was no antibody response to O and H antigens

These repeated infections could be attributed to gamma globulin deficiency and a concomitant poor antibody response Whether the syndrome is a congenital or an acquired defect in gamma globulin synthesis is difficult to ascertain With increased application of filter paper electrophoresis more cases of agammaglobulinemia should be recognized

Specific Agglutination of Treponema Pallidum by Serums from Rabbits and Human Beings with Treponemal Infections Attempts to demonstrate specific antibodies to Treponema pallidum led to the discovery of the Wassermann reaction and other standard serologic tests for syphilis However it is now generally believed that these tests not only do not reveal a specific antibody but that they sometimes give positive reactions with serums from persons with no history of syphilis or other treponemal disease The treponemal immobilization test provided for the first time an in vitro method for detection of specific antibodies However the technical difficulties of this test have limited its usefulness and a simple specific immunologic test is needed

Paul H Hardy Jr and E Ellen Nell[4] (Johns Hopkins

(3) A M A A h. Int Med 95 33 36 Ja y 1955
(4) J E pe Med 101 367 382 April 1955

suggests a causal relationship An interesting corollary would be that all bacteria are equally sensitive to penicillin in the sense that a given amount of bound penicillin has the same effect on all cells sensitive or insensitive Difference between a penicillin insensitive and a highly sensitive organism would be in amount of penicillin which must be added to the outside fluid to effect the same lethal degree of combination This has actually proved to be the case At lethal concentrations all strains studied had bound the same amount From 900 1 250 molecules of penicillin can be bound per cell without demonstrable effect on rate of growth A slight increase in bound penicillin 1 500 1 700 molecules per cell results in bacteriostasis It appears that all bacteria contain one or more penicillin vulnerable components capable of combining with 1 500-4 000 molecules per cell that as much as one third to two thirds of these components can be inactivated without demonstrable effect on cell function and that death results when they are almost saturated with the antibiotic In penicillin sensitive cells these components are highly reactive

Intimately related to mode of action and to the binding phenomenon is development of resistance to penicillin Experimental evidence indicates that when change from sensitivity to resistance occurs it reflects a spontaneous mutation and selective multiplication of that rare mutant in the presence of the antibiotic

The miraculous aspect of antibiotics is not that they kill bacteria but that they do so usually without killing the host Mammalian cells are resistant to penicillin either because they do not contain penicillin vulnerable components or because these components have a very low order of reactivity'

[I find it hard to select each year s batch of article without including one or more of Eagle s contributions Although as he points out there is still too little information about the mode of action of antibiotics his own contributions to the subject are some of the best —Ed]

Studies of Microbial Populations Artificially Localized In Vivo II Difference in Antityphoidal Activities of Chloramphenicol and Chlortetracycline In general if a particular drug can exert powerful antimicrobial action in vivo against certain pathogens it will be similarly effective against all pathogenic bacteria inhibited by low concentrations of the drug in vitro Notable exceptions include typhoid fever bru

function and whose mode of action is still unknown after years of successful use Detailed exposition of how these agents cause death of the cell would contribute materially to understanding of cellular function both bacterial and mammalian and might lead to more effective treatment

The mechanism by which the agent effects cure in the infected host and its chemical action on the bacterial cell are of paramount importance To say that penicillin cures infection primarily by direct bactericidal action is not to deny that host defenses are important but these two mechanisms apparently operate independently Inability of penicillin treated bacteria to transport essential glutamic acid across the cell boundary is neither the regular nor probably the primary cytopathogenic effect It was recently found that in cell free staphylococcic extracts able to synthesize protein penicillin at a relatively low concentration (1 µg /ml) inhibited formation of an adaptive enzyme galactosidase as well as synthesis of ribonucleic acid Whether a similar interference with synthetic processes is the basis of antibacterial action is unknown

Another unexplained fact is that penicillin kills bacteria in vitro only if they are in an environment which permits active metabolism and growth It is conceivable that penicillin blocks a metabolic reaction and thereby leads to accumulation of a metabolite *toxic in excess that occurs only in the* actively metabolizing cell A second possibility is that if organisms are exposed to penicillin in a growing medium after penicillin has inactivated the postulated vulnerable and essential enzyme the cell may attempt to replace it by synthesizing new enzyme from precursor substances The newly formed enzyme would then also be inactivated and this would continue until the cell had exhausted the precursors thereby becoming nonviable

With some bacteria high penicillin concentrations are less rapidly effective than a lower optimal concentration If a suspension of bacteria is exposed to radioactive penicillin under standard conditions and if at varying periods bacteria are centrifuged out washed and their radioactivity measured penicillin is found to be rapidly bound and concentrated particularly with the more sensitive strains Correlation between sensitivity and ability to combine with penicillin

in chemotherapy of typhoid fever in contrast to treatment of other susceptible intracellular infections in which a more uniform response to these compounds has been noted

Effect of Heparin and Penicillin in Combination on Local Septic Foci Study Based on Animal Experiments is reported by Stig Borgstrom Anders Muren and Ingemar Erici[7] (Lund Sweden) Besides its coagulation inhibiting or thrombostatic effect in both man and animals heparin also possesses a fibrinolytic action not seen in vitro through which fresh thrombi may be resolved and made to disappear completely Thrombolytic effect of heparin ceases on organization of the thrombus Sandblom *et al* suggested that the power of the body to combat infection might gain better access to a focus of infection if thrombus formation of small vessels and deposition of fibrin in surrounding tissues were decreased

The authors suggest that the body s capacity to wall off a septic focus by thrombosis of vessels and fibrin deposition in tissues impedes healing of the septic process if resistance of the organism against infection is sufficient to counteract the invasion If these powers are too weak walling off will contribute toward the restriction and healing of the process but then the protective powers may be so strengthened by a suitable antibiotic that swifter healing will also occur if thrombosis of the small vessels and deposition of fibrin in surrounding tissue are decreased

Experiments were performed on white female rabbits weighing about 2 kg The penicillin preparation contained one fourth sodium salt and three fourths procaine penicillin Only one bacterial strain was used penicillin sensitive Staphylococcus aureus Fleming The rabbits were given intracutaneous injections of staphylococcus suspension with undiluted bouillon culture and with dilutions of 1 10 1 100 and 1 1 000 As pronounced heparinization of the animals was desired 50 mg heparin was administered in each dose Results showed that heparin and penicillin in doses that individually afford no demonstrable effect will decrease the size of local septic foci in combination

Actual time for administration of heparin during penicillin treatment is apparently important During the first hours

(7) A t h nd 108 114 124 1954

cellosis and tuberculosis Although causative agents have been inhibited in vitro by low concentrations of several drugs only a few compounds have been significantly effective against these diseases in patients or experimental animals e g streptomycin has inhibited Salmonella typhosa in vitro in concentrations comparable on a weight basis to those of chloramphenicol yet the former has been notably ineffective in treatment of typhoid fever Similar results have been noted for streptomycin in brucellosis subtilin in experimental tuberculous infections and chlortetracycline in typhoid fever

Charles A Werner Walsh McDermott Carol Adams and Rebeckah DuBois[6] (New York Hosp Cornell Univ) report a study on comparative antityphoidal activities of chlortetracycline and chloramphenicol to explain their different therapeutic effects in typhoid fever In vitro minimal inhibitory concentrations of the two drugs for S typhosa were determined in parallel by the conventional serial dilution method In vivo studies were carried out in cats and serum concentrations after various oral and intravenous doses of the two drugs were correlated with suppression of growth of typhoid bacilli encased in triple layered agar disks inserted into the peritoneal cavities of the animals The bacilli were found to be subsisting directly on nutriments supplied by the host in a state more closely approximating true parasitism than is possible in vitro The agar disks were readily penetrated by both drugs from extracellular fluid of the peritoneal cavity

Essentially equivalent concentrations of the two compounds exerted comparable bacteriostatic effect on typhoid bacilli in vitro and in vivo Doses of chlortetracycline required to provide concentrations in the extracellular fluid inhibitory for S typhosa were significantly greater than those of chloramphenicol and were greater than those ordinarily used clinically

Results indicate that one explanation for the difference in therapeutic activities of chlortetracycline and chloramphenicol in typhoid fever may be the difference in the drug host rather than the drug parasite relationships of the two compounds This drug host difference may be a critical factor

(6) J Clin Invest. 33 753 758 May 1954

Clinical use of procaine penicillin preparations in preference to sodium penicillin is based largely on the contention of Eagle *et al* (1950) that the curative effect depends primarily on concentration of penicillin in the blood and the total time it remains at effective levels However the present experiments demonstrated that the curative effect following one injection of sodium penicillin continues long after the penicillin falls below a detectable level in the blood and is as good as that obtained after injection of procaine penicillin Total duration of an effective level of penicillin apparently is not the sole factor in determining the curative effect Two factors to be considered are maximum concentration of penicillin in the blood and defense mechanisms of the host Maximum concentration after injection of sodium penicillin is five times greater than that after injection of procaine penicillin The former would therefore give a much higher concentration in the staphylococcic lesions and so produce a greater effect but over a relatively shorter period

The streptococcic infection used by Eagle and his co workers and the staphylococcic infection used in the present experiments behave differently Mice have little or no immunity to hemolytic streptococci so that experimental infection is rapidly fatal conversely they are so resistant to staphylococcic infection that even large inoculations produce only a local lesion with a low mortality rate

Applications of these findings to penicillin treatment in man is difficult but experimental staphylococcic infection resembles conditions in man more closely than streptococcic infection because most human infections elicit some response by body defenses Hence penicillin treatment should be given in a manner to provide maximum aid to body defenses The results suggest that this can be done as well with sodium penicillin as with procaine penicillin even when doses are infrequent

It is not clear whether sodium penicillin or procaine penicillin gives better results in clinical treatment Probably prolonged blood levels obtained with procaine penicillin are valuable when only one dose can be given as in mass treatment of syphilis and yaws Conversely even when the drug can be given only infrequently it has yet to be proved whether prolonged low blood levels provided by procaine penicillin are more efficacious than the short lasting but

after inoculation with bacteria the effect of penicillin is not enhanced by simultaneous administration of heparin probably because fibrin deposition in tissues and thrombosis of small vessels are as *yet* so slight that penicillin is able to penetrate to the focus of infection and exert its effect To establish the effect of the penicillin heparin combination a fairly well balanced ratio between dose of penicillin and quantity of bacteria inoculated is necessary If a greater or lesser dose of penicillin is given no certain increase in effect of simultaneous administration of heparin is established Even though heparin lowers the size of the smallest penicillin dose registrable there must be a level below *which no* effect of penicillin+heparin is registrable With greater doses of penicillin effect of this antibiotic alone is so strong that no additional effect appears on administration of heparin in these experiments of short duration

[Present treatment of localized pyogenic infections is not altogether satisfactory Results of investigations of this type may help us to achieve better results Before the advent of penicillin many people held the opinion that heparin had value as an adjunct to sulfonamides in therapy of staphylococcic infection—Ed]

Comparison of Sodium and Procaine Penicillin in Treatment of Experimental Staphylococcic Infection in Mice There is still a division of opinion regarding administration of penicillin in treatment of infections The question has been renewed with the introduction of depot preparations which have the advantage over sodium penicillin of prolonging absorption from the injection site so that effective concentrations are maintained much longer F R Selbie[8] (Univ of London) performed experiments to determine the comparative effects of these penicillin preparations on infections with Staphylococcus pyogenes in mice In each experiment four groups of six mice weighing about 30 Gm were inoculated intramuscularly with 0 2 ml of an 18 hr culture of this organism in tryptic digest broth The first group was untreated and the others were treated with sodium salt of penicillin G procaine penicillin G in arachis oil containing 2% *aluminum stearate or an aqueous suspension* of procaine penicillin G

All three penicillin preparations significantly reduced the size of the swellings but none were demonstrably better than the others

(8) B r M J 1 1350-1353 J n 12 1954

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high blood levels provided by sodium penicillin in treatment of infections generally amenable to this therapy

[The debate goes on over the relative value of soluble and depot preparations of penicillin Probably in most clinical situations it is not decisive since other factors e g the host s defense mechanisms the character of the infection and the mass of infecting organisms are also important However most experienced clinicians seem to prefer soluble penicillin in critical cases.—Ed]

Effect of Antibiotic Therapy on Susceptibility to Experimental Enteric Infection Common complications of antibiotic therapy are so called secondary or superimposed infections in the oropharynx or bowel caused by microorganisms insensitive to the drug administered The antibiotic is presumed to render such sites vulnerable to implantation of contaminating organisms by suppressing or eliminating some of the normal inhabitants i e by disturbing the ecology of normal microflora C Phillip Miller Marjorie Bohnhoff and Barbara L Drake[9] (Univ of Chicago) performed experiments on mice to determine whether normal bacterial flora in the intestinal tract offers any protection against one of its natural enteric infections and if so to what degree

Mice were inoculated with a streptomycin resistant strain of Salmonella enteritidis by mouth Streptomycin was also given orally in most experiments the day before inoculation Mice used were known to be quite resistant to salmonella carriers were found among them but illness or death due to salmonella infection was infrequent

Among controls inoculated with 420 000—the largest inoculum used—only one mouse became definitely infected Results on streptomycin treated mice were in sharp contrast These mice received 50 mg streptomycin orally the day before inoculation Definite infection occurred in all inoculated with 420 and 42 salmonella and in two of five inoculated with approximately 4 salmonella Thus susceptibility was greatly enhanced by a large dose of streptomycin given orally 24 hours before inoculation Between 100 000 and 1 000 000 salmonella were required to infect 50% of the controls but less than 10 sufficed to infect 50% of the mice given streptomycin The susceptibility did not persist unchanged but diminished as the interval between treatment

(9) T A Am Phy icia s 67 156 161 1954

and inoculation was lengthened i e effect of streptomycin gradually wore off but was still detectable five or six days after treatment

The effect of streptomycin on resistance to inf t on was not the result of toxic action Much larger doses gave rise to no signs of toxicity This is not surprising because little if any streptomycin is absorbed from the gastrointestinal tract Thus its effect must have been due to its local action within the intestinal lumen where it caused a large reduction in the bacterial population With this change in normal microflora conditions within the lumen became more favor able for establishment of salmonella infection The results support the suggestion by several workers that such com plicating infections come about through disturbance of normal microflora

[A nicely conceived and convincing experimental demonstration of superinfection due to antibiotic therapy —Ed]

UNTOWARD EFFECTS OF ANTIBIOTICS

Fatality Following Penicillin Injection which occurred almost instantaneously in a seemingly healthy young man with no apparent allergic background is reported by Sey mour Fisher[1] (V A Hosp Phoenix Ariz)

Man 28 hospitalized for disarticulation of a hammer toe re ceived a low spinal anesthesia with 150 mg procaine at 9 15 a m operation was begun at 9 23 Shortly after return to the ward (at 10 05) he was given a prophylactic injection of 300 000 units of aqueous penicillin intramuscularly In less than five minutes he com plained of chest pain then shortness of breath Within seconds he became cyanotic and pulseless At 10 10 a m epinephrine (1 cc) was given intramuscularly and artificial respiration was started This was followed by the use of coramine ® oxygen epinephrine to the heart and finally a mechanical respirator He was pronounced dead at 11 a m

An additional history was obtained showing that on two occasions the patient had had evere reactions to novocain ® Penicillin (type unknown) had been given several times for minor illnesses without reactions

Autopsy findings as in other reported cases were not significant The presence of increased subcutaneous fat also reported in a similar case by Christenson *et al* may have some significance since reac tions of all types tend to occur oftener in persons with fat diathesis

(1) A I t M d 40 1227 1230 J 1954

Fisher agrees with those who state that antibiotics should be used only when indicated and not as prophylactic or shotgun treatment

Pseudomembranous Enterocolitis Following Antibiotic Therapy for Pneumonia Report of Case is presented by Gilbert H Friedell and Emil Paige² (Salem Mass)

Girl 12 had fever for four days and nonproductive cough for one day before hospitalization Percussion showed impaired resonance over left lung base with diminished breath sounds and dry rales on auscultation She was given 400 000 units of penicillin intramuscularly twice daily Two days later roentgenogram showed pneumonic consolidation in left lower lobe With penicillin for eight days temperature was 100 103 F and left lung changes persisted A second x ray showed some resolution of the original process but extension to the lingular portion of the upper lobe Penicillin was discontinued and 125 mg oxytetracycline was given orally every six hours with 0 5 Gm streptomycin/day intramuscularly In two days temperature returned to normal the left lower lung field cleared and striking clinical improvement was noted After six days of continued therapy she was afebrile and clinically well and medication was stopped preparatory to discharge That evening she had a sudden watery bowel movement cramps and vomiting that increased the following day Temperature rose to 100 F and she was irritable and complained of a sore throat She became critically ill in about 36 hours was dehydrated despite fluids parenterally and grew progressively worse with terminal temperature 107 4 F X ray of chest showed almost complete resolution of the pneumonic process Blood chloride was 94 mEq/L and plasma CO content 17 mEq/L Leukocytes numbered 15 000 with 68% neutrophils She went into shock and died despite plasma and cortisone therapy

At autopsy gastric and duodenal mucosa was yellow green From the distal portion of the duodenum to the cecum the surface was covered by bright yellow pseudomembrane easily separable from the underlying wall No ulceration was seen The mucosa of the colon was also bright yellow but there was no definite pseudomembrane or ulceration Microscopically areas of superficial mucosal necrosis were seen in the colon in some instances with surface exudation and sections of jejunum and ileum revealed acute mucosal inflammation with some necrosis of mucosal glands and stroma. Extent and severity of mucosal involvement and histologic process varied somewhat despite fairly uniform gross appearance Many sections showed diphtheritic type pseudomembrane containing several clumps of bacteria with necrosis and conspicuous acute inflammatory cell infiltration of the upper third to one half of the mucosa (Figs 1 and 2) In some sections necrosis and cellular infiltrate involved the entire thickness of the mucosa

Without known gastrointestinal disease or surgery the

(2) Am J Clin Path 24 1159 1164 October 1954



F g 1 (t p) —*C* ect f *j j* um how g *mpl t ly l* p e do-m mb n ry g d g e f m l nd p m t bm l d m Hem t yl n ×10

F g 2 (bott m) —Magn fi t of m ked *r* F gure 1 N t e mplet d tru t on f mu l l m t n ent w th m p t on f gland on h s d d *foc l gg g t f b t H m t xyl* ×*36*

(Cou t y f F d ll G H d P g E Am J Cl P th 24 1159 1164 O t be 1954)

Fisher agrees with those who state that antibiotics should be used only when indicated and not as prophylactic or shotgun treatment

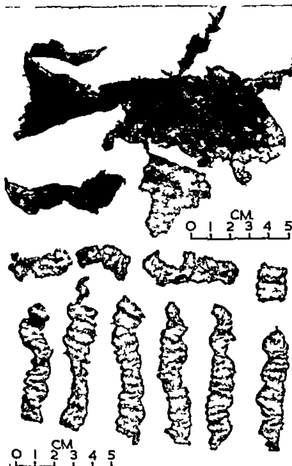
Pseudomembranous Enterocolitis Following Antibiotic Therapy for Pneumonia Report of Case is presented by Gilbert H Friedell and Emil Paige[2] (Salem, Mass)

Girl 12 had fever for four days and nonproductive cough for one day before hospitalization Percussion showed impaired resonance over left lung base with diminished breath sounds and dry rales on auscultation She was given 400 000 units of penicillin intramuscularly twice daily Two days later roentgenogram showed pneumonic consolidation in left lower lobe With penicillin for eight days temperature was 100 103 F and left lung changes persisted A second x ray showed some resolution of the original process but extension to the lingular portion of the upper lobe Penicillin was discontinued and 125 mg oxytetracycline was given orally every six hours with 0 5 Gm *streptomycin/day intramuscularly* In two days temperature returned to normal the left lower lung field cleared and striking clinical improvement was noted After six days of continued therapy she was afebrile and clinically well and medication was stopped preparatory to discharge That evening she had a sudden watery bowel movement cramps and vomiting that increased the following day Temperature rose to 100 F and she was irritable and complained of a sore throat She became critically ill in about 36 hours was dehydrated despite fluids parenterally and grew progressively worse with terminal temperature 107 4 F X ray of chest showed almost complete resolution of the pneumonic process Blood chloride was 94 mEq/L and plasma CO content 17 mEq/L Leukocytes numbered 15 000 with 68% neutrophils She went into shock and died despite plasma and cortisone therapy

At autopsy gastric and duodenal mucosa was yellow green From the distal portion of the duodenum to the cecum the surface was covered by bright yellow pseudomembrane easily separable from the underlying wall No ulceration was seen The mucosa of the colon was also bright yellow but there was no definite pseudomembrane or ulceration Microscopically areas of superficial mucosal necrosis were seen in the colon in some instances with surface exudation and sections of jejunum and ileum revealed acute mucosal inflammation with some necrosis of mucosal glands and stroma Extent and severity of mucosal involvement and histologic process varied somewhat despite fairly uniform gross appearance Many sections showed diphtheritic type pseudomembrane containing several clumps of bacteria with necrosis and conspicuous acute inflammatory cell infiltration of the upper third to one half of the mucosa (Figs 1 and 2) In some sections necrosis and cellular infiltrate involved the entire thickness of the mucosa

Without known gastrointestinal disease or surgery the

(2) Am J Clin Path 24 1159 1164 October 1954



F g 3 (t p) —M mbra f m tomach
Fig 4 (bott m) —M mb a e f m m ll t pa sed f
(C tesy f W ll m E La et 2 999 1000 N 13 1954)

tive pressor agent in this case its early use contributing largely to recovery The antibiotic responsible for enterocolitis should be withdrawn immediately and theoretically the Staph pyogenes can be eliminated by any other antibiotic to which it is still sensitive At present erythromycin is the antibiotic of choice but oral administration alone may

antibiotics are implicated as directly or indirectly responsible for the enterocolitis Interval between cessation of penicillin and onset of gastrointestinal symptoms suggests that it was etiologically less significant than oxytetracycline and streptomycin The fatal outcome probably resulted from a complication of therapy and not from initial illness

[This fatal complication of antibiotic therapy developed and progressed very rapidly and probably the death could not have been averted by any therapy nevertheless it would have been worth while to attempt to control the presumed staphylococcic infection by administration of erythromycin See following case —Ed]

Staphylococcic Pseudomembranous Enterocolitis Complicating Treatment with Aureomycin is discussed by Eirian Williams[3] (London Hosp) The tetracycline derivatives have serious side effects These antibiotics particularly oxytetracycline have caused many deaths from fulminating staphylococcic enterocolitis

Girl 15 underwent suprapubic cystotomy for removal of hair pin she had inserted into her bladder She was given 1 Gm elkosin® (6 [p aminobenzene sulfonamido] 2 4 dimethylpyrimidine) orally every six hours because of symptomless pyrexia A week later this was supplemented by 0 25 Gm chlortetracycline orally every eight hours for four days After two days she became afebrile but discharge was deferred due to sudden diarrhea and vomiting which became progressively severe Two days later she became semicomatose collapsed and was in severe shock Diagnosis of staphylococcic enteritis was confirmed by finding pus and gram positive cocci in the feces culture yielded profuse growth of Staphylococcus pyogenes sensitive to erythromycin and neomycin but insensitive to penicillin streptomycin chloramphenicol chlortetracycline and oxytetracycline

Erythromycin was given orally intravenously and intramuscularly The following morning a large membrane cast consisting of gastric mucosa was vomited (Fig 3) and during the day portions of small gut mucosa were recovered from the feces (Fig 4) Vomiting ceased her mental state and peripheral circulation improved in a day or two but fecal incontinence persisted for several days

Diarrhea appears suddenly on the third or fourth day of antibiotic treatment and the feces are copious and green Diagnosis can be confirmed by microscopic examination of feces which contain pus and staphylococci in profusion Staphylococcic enterocolitis constitutes an emergency demanding prompt and vigorous treatment Shock requires administration of blood or plasma and if hypotension is extreme of adrenal extracts Nor adrenaline was an effec

(3) Lancet 2 999 1000 No 13 1954

isfactory immunity and (3) nasal carriage Abundant evidence suggests that staphylococci in the anterior nares provide the source of infection and of reinfection after local treatment in most staphylococcic skin diseases The anterior nares harbor staphylococci in greater profusion than any other part of the body and in a high percentage of the population Sterilization of the anterior nares must be a corollary to other treatment methods if the responsible bacteria do emanate from the nasal flora

A search of the literature revealed no report of comparison of strains from skin lesions and nose by phage typing Hence Tulloch collected 73 pairs of cultures from the noses and lesions of patients with sycosis barbae furunculosis folliculitis and infective eczematoid dermatitis Eighteen pairs were not typable and in four only one strain was typable In 45 (88 2%) of the 51 typable pairs both strains were identical The commonest groups of phage types were the 6/7/47/54 group and the 3b/3c group which together accounted for two thirds of the typable strains

These findings provide final proof of the identity of staphylococci isolated from a skin infection and from the anterior nares of the same patient and suggest that local treatment alone is likely to be followed by a relapse unless accompanied by an attack on the nasal flora A preparation useful for this purpose is the tyrothricin solution described by MacKee *et al* sodium mixed alkyl sulfonate 1 0% tyrothricin 0 1% propylene glycol 10 0% distilled water 88 9% Alternatively an aqueous solution of penicillin (1 000 units/ml) is effective and no instances of sensitization have been observed from its use in this way These solutions are best administered with an atomizer but a suitable cream containing 0 1% tyrothricin or 1% chlortetracycline may also be used Tyrothricin is especially suitable for this purpose since it is never administered parenterally and hence the risk of producing resistant strains may be ignored

[The matter of ridding the patient of his nasal carrier state seems to be a key point in treatment of recurring furunculosis —Ed]

Influence of Antibiotics on Origin of Small Colonies (G Variants) of Micrococcus Pyogenes Var Aureus was investigated by Robert I Wise and Wesley W Spink[6] (Univ

(6) J Cl I t 33 1611 16 D b 1954

be unsatisfactory because of vomiting Bacitracin and neomycin orally may also be effective

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STAPHYLOCOCCIC INFECTION

Studies on Staphylococci from Hospital Patients I Predominance of Strains of Group III Phage Patterns Which Are Resistant to Multiple Antibiotics In a study of 516 strains of Staphylococcus aureus (Micrococcus pyogenes var aureus) principally cultured from nose throat and rectum of staphylococci carriers at Bellevue Hospital in 1953 and 1954 Vernon Knight and Anna R Holzer[4] (Cornell Univ) found that 65% were resistant to chlortetracycline oxytetracycline streptomycin and penicillin Over 90% of these drug resistant strains were of phage group III patterns Strains of staphylococci were of intermediate degrees of susceptibility to chloramphenicol and nearly all were highly susceptible to erythromycin

In contrast 55 similar strains collected in 1932 38 were to a large extent susceptible to penicillin and were all inhibited by low concentrations of the tetracyclines and erythromycin They were of intermediate degrees of susceptibility to streptomycin and chloramphenicol and only 20% were in phage group III

Few staphylococci of group III phage patterns resistant to multiple antibiotics were isolated on admission from staphylococci carriers but thereafter these hospital staphylococci rapidly replaced other strains of staphylococci in patients treated with tetracyclines Cultures from patients treated with penicillin underwent a similar but significantly less rapid change whereas only a moderate increase in percentage of strains of hospital staphylococci occurred among those who received no antibiotics

Nasal Carriage in Staphylococcic Skin Infections According to L G Tulloch[5] (Bristol Royal Hosp) treatment of chronic staphylococcic infections of the skin is seldom satisfactory even with vigorous antibiotic administration Main reasons for this are (1) constitutional factors i e hormonal imbalance especially androgen excess (2) unsat

(4) J Clin Invest 33 1190 1198 September 1954
(5) Brit M J 2 912 913 Oct 16 1954

strain The characteristics of the reverted forms were the same as those of the parent cells except the virulence of the reverted forms was increased in some instances

Compared to the parent strain the G variants had less hemolytic activity produced less coagulase and had more demanding nutritional requirements They were less virulent and remained viable in tissues of apparently normal animals Bacteriophage typing of the parent cells related G forms and reverted large colonies showed a genetic relation which ruled out contamination

The presence of G colonies in human material was studied by examining with magnification the original cultures of about 500 specimens of blood exudate urine and other body fluids G colonies were isolated 10 times from eight patients of whom seven had been treated with an antibiotic or sulfonamide when the isolates were made The cultures gradually reverted to colonies of normal size Little is known concerning the role of such bacterial variants in disease

Under in vitro conditions there is an optimal concentration of antibiotic for recovering G colonies The G forms are two to eight times more resistant than the parent cells The slow growing G variants can thus be isolated most readily with concentrations of antibiotic that eliminate or inhibit growth of the normal forms This optimal concentration falls within a narrow range Optimal concentrations of antibiotics for survival of G colonies may occur in human tissues during therapy of staphylococcic infections and under these conditions avirulent small colony variants may be selected out and remain undetected Following cessation of therapy reversion to a virulent form may occur and relapse of infection ensue Careful bacteriologic studies should therefore include search for G colonies after apparently successful treatment in patients with staphylococcic disease

[These small atypical colonies must be looked for carefully in the clinical bacteriology laboratory Perhaps failure to identify them explains some of the unsatisfactory experiences we have had in management of staphylococcic infections —Ed]

Staphylococcic Endocarditis Some Clinical and Therapeutic Observations on 38 Cases are made by A M Fisher H N Wagner Jr and R S Ross[7] (Johns Hopkins

(7) A M A A h I t M d 95 427 437 M r h 1955

of Minnesota) Bacteria produce small colony variants especially in unfavorable environments e g chemicals antibiotics and aging

PROCEDURE —Coagulase positive staphylococci were mixed with penicillin streptomycin chloramphenicol bacitracin carbomycin and oxytetracycline in concentrations of 0 1 1 10 and 100 units or µg /ml and erythromycin in concentrations of 0 25 2 5 5 10 20 40 and 80 µg /ml The number of strains tested with each antibiotic was penicillin 20 erythromycin 10 carbomycin 9 bacitracin 9

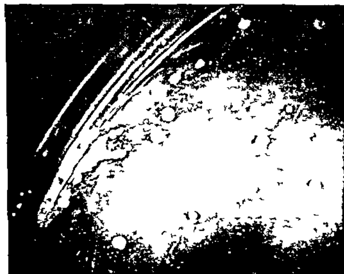


Fig 5 —C mpa t e f G l s a d no m l d l ge c lon f taphylococc (Courtesy f W R. I d Sp k W W J Cl I vest 33 1611 1622 December 1954)

streptomycin 13 oxytetracycline 8 and chloramphenicol 8 Fifteen stable G cultures were obtained with penicillin 2 with erythromycin 3 with carbomycin and 4 with bacitracin none was isolated with streptomycin and chloramphenicol

The G colonies were translucent and nonpigmented had a diameter of less than 0 1 mm and were seen with difficulty except by reflected light or with magnification (Fig 5) They could be easily overlooked When cultivated without antibiotics they reverted either slowly or rapidly to colonies of normal appearance Some cultures reverted almost com pletely within 24 hours others remained stable for a month or more The rate of reversion was characteristic of the

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Staphylococcic Endocarditis Some Clinical and Therapeutic Observations on 38 Cases are made by A M Fisher H N Wagner Jr and R S Ross[7] (Johns Hopkins

(7) A M A A h I t M d 95 427 437 M h 1955

Univ) The 38 cases fulfilled diagnostic criteria for staphylococcic endocarditis 25 being proved at autopsy and 13 considered clinically certain They were divided into three periods 22 seen in 1933-43 when no established antibiotic therapy was available 3 seen in 1944-48 the time of effective penicillin therapy with most staphylococci sensitive to that agent and 13 seen in 1949 53 when penicillin resistance became a factor Penicillin resistance was found in 5 of 12 cases in this period

The striking fall in incidence in 1944-48 parallels a similar decrease in all staphylococcic bacteremia cases during that time This decrease may have been due to availability of penicillin for therapy of all staphylococcic infections and to sensitivity of a high percentage of strains to penicillin Thus infections were more readily controlled as they developed and less likely to invade the blood stream

Patients in the third period were of particular interest because of special problems in diagnosis and therapy Diagnosis of acute bacterial endocarditis may be difficult to establish In one patient (not included in the series) with known valvular disease and staphylococcic septicemia for several days autopsy showed no evidence of bacterial endocarditis Onset and course may simulate the subacute form rather than the more usual fulminating course Five patients had a subacute course for a month or more before hospitalization The white cell count may also be misleading instead of leukocytosis a normal or low count is found in some instances

As in subacute bacterial endocarditis there is danger of extensive valve damage followed by myocardial failure even though the infection may be eradicated In three patients myocardial failure developed One died during treatment of two in whom infection cleared one was in failure at discharge and one died in failure 18 months later

Prolonged treatment with massive doses of penicillin together with other antibiotics resulted in control of infection in 7 of the 13 patients Only one patient in each of the first two groups survived Of interest is the unexpected finding that most strains studied in 1949 53 were sensitive to penicillin Three of the five patients with resistant organisms survived Organisms in these three cases were resist

ant to less than 12 5 62 5 and 50 units of penicillin yet massive amounts of penicillin with large doses of erythro mycin led to favorable outcomes In one of these patients who had a history of penicillin sensitivity penicillin was withheld for a time During erythromycin and chloram phenicol therapy blood cultures again became positive and there was clinical relapse prompt response followed addi tion of penicillin Such examples suggest that regardless of results of in vitro tests for penicillin sensitivity treatment should include massive doses of penicillin which can be given in almost unlimited amounts and is primarily bac tericidal No patient was cured by any combination of anti biotics which did not include penicillin

Acute Staphylococcic Enterotoxin Food Poisoning in a Victorian Town E J Crowe[8] (State Health Dept Mel bourne) reports an outbreak in October 1952 affecting about 20% of the persons who lunched at the town s annual agri cultural show Symptoms began approximately three hours later and included nausea abdominal pain diarrhea vomit ing and in more severe cases cramp collapse and cyanosis At the peak patients lay around the showgrounds in the garden of the doctor s house and in the hospital compound or vomited from their cars into the street gutters Many received ambulant treatment (0 3 gr morphine) Of about 80 patients 14 were hospitalized All recovered in 48 hours the majority in 24

Dramatic onset incubation period of three to four hours brief duration typical signs and symptoms and rapid recov ery without specific treatment indicated ingestion of pre formed toxin rather than bacterial poisoning agent probably being staphylococcic enterotoxin Phage typing showed that the staphylococcus isolated from the nose of a food preparer was identical with that isolated from inside an empty green pea tin and the rectal swab of a patient The food handler had ample opportunity for accidentally con taminating various food items and the empty green pea tin probably was contaminated by other waste food Crowe believes that the outbreal was due to a coagulase-positive staphylococcic enterotoxin

(8) M J A t l 1 468 470 M 7 1954

Unaltered Penicillin Susceptibility of Streptococci Study of Alpha Hemolytic Streptococci Causing Endocarditis 1944 to 1954 Alpha hemolytic (viridans) streptococci the commonest cause of subacute bacterial endocarditis are also normal inhabitants of the human throat and gastrointestinal tract and are inevitably exposed to penicillin each time it is used in treatment Hence conditions favorable to emergence of drug resistant strains have been continuously operative for the past decade Carl A Berntsen Jr[9] studied penicillin susceptibilities of 105 strains of alpha streptococci isolated from patients with subacute bacterial endocarditis at the New York Hospital Cornell Medical Center during the past 10 years Twenty six lyophilized strains isolated in 1944 47 were re examined and compared with 22 selected recently isolated strains results showed good agreement thus establishing comparability of technics used for testing penicillin susceptibility throughout the different time periods Additional strains studied were 68 isolated in 1947-54

Average values for penicillin susceptibility of strains isolated during the more recent time period were not significantly different from values recorded for the 1944-47 period Extremes of inhibitory concentrations were within one tube dilution of the extremes 0 01 0 4 unit of penicillin/ml Four strains of alpha streptococcus recovered in 1944 and 12 recovered after 1951 showed no significant difference with respect to ability to survive nine days exposure to 2 units of penicillin/ml

Absence of change in such a ubiquitous organism as the alpha streptococcus emphasizes that the problem of increased prevalence of penicillin resistant micrococci does not necessarily apply to all penicillin susceptible microbial species

[*Good news* since some clinicians have been expressing the opinion that bacterial endocarditis due to resistant organisms is a more frequent occurrence now In view of the above figures that sort of impression may well represent the fallacious nature of clinical recollections —Ed]

Type 12 Streptococci Associated with Acute Hemorrhagic Nephritis A relation between acute glomerulonephritis in

(9) J A M A. 157 331 333 Jan 2 1955

children and young adults and preceding streptococcic infections has long been recognized and Rammelkamp *et al* have recently presented evidence suggesting that the sequela of nephritis is largely confined to infections with type 12 group A hemolytic streptococcus The postulate is that the epidemiology of acute hemorrhagic nephritis is basically that of certain strains of nephritogenic group A streptococci and the evidence incriminates type 12

Mary J Wilmers A C Cunliffe and R E O Williams[1] (London) investigated two groups of patients with clinically typical acute glomerulonephritis Of the 31 patients studied 28 (90%) showed type 12 group A streptococci Although type 12 is one of the commonest streptococci now found in England and Wales its prevalence in throats of patients with acute glomerulonephritis is too great to be explained by chance The findings suggest that in England as in America there is a close relation between acute glomerulonephritis and infection with type 12 streptococci

ERYSIPELOID

Five Hundred Cases of Erysipeloid Eli Nelson[2] (Denver) believes that practitioners and internists should be more aware of this cutaneous disease caused by Erysipelothrix rhusiopathiae Too many physicians make a diagnosis of cellulitis and are too prone to incise the lesion but surgery is not necessary The disease should not be confused with human erysipelas of streptococcus origin The causative agent of swine erysipeloid is a slender small straight or curved rod a gram positive nonmotile non spore forming microaerophilic bacillus It may be smooth or rough and may form branching filaments of variable length The organism can usually be isolated from a small section of skin but not from serum or material from the lesion

Of 500 patients seen by Nelson 260 worked in packing houses 144 in rendering plants 84 in hide establishments and a few in butcher shops restaurants and fish stores The usual history was that of a small cut which did not bleed an

(1) L et 2 17 18 J ly 3 1954
(2) Rocky M t M J 52 40 4 J y 1955

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(9) J A M A 157 331 333 Jan 22 1955

may be insidious or sudden Usually the patient complains of general malaise headache and anorexia for a few hours followed by rigor fever to 101 103 F and local pain Skin in or near the site of trauma begins to turn dark red and spreads centrifugally with an irregular border and without elevation of the skin margin (contrary to true erysipelas) Varying degrees of swelling accompany the cellulitis The acute phase lasting three to seven days is followed by desquamation

Diagnosis is based on history of repeated attacks of unilateral acute cellulitis of the same area of the foot or leg with typical symptoms Laboratory study helps little as smears or cultures from the skin lesions rarely demonstrate fungi or hemolytic streptococci Sulfonamides and antibiotics have no effect on the cellulitis granting that it is an allergic reaction to a remote antigen but may be used for secondary infection

The only treatment during the acute attack is bed rest elevation of the affected leg and intermittent application of warm saline or boric acid packs For active skin lesions immersion in 0 25% chlorazene® solution for 20 minutes three times daily followed by thorough drying is effective If recurrence of the fungous infection is prevented there should be no future attacks of erysipeloid cellulitis

[This is of course a very different erysipeloid from the disease described in the preceding article The clinical picture described here is certainly not rare and perhaps the author is correct in his belief that fungous infection is important in the pathogenesis It still seems possible to me that some of these patients have recurrent bacterial infections The fact that the course is self limited does not rule out the possibility —Ed]

SALMONELLOSIS

Salmonella Meningitis in Infancy results in high mortality In cases reviewed by Henderson in 1948 87 5% were fatal and in cases cited by Beene in 1951 most of which had occurred after availability of antibiotics mortality was 82 7% However the most recent cases treated with broad spectrum antibiotics seemed to show increased survival Esmond S Smith[4] reviews 10 recently reported cases and adds 6 of his own to show the effects of chloramphenicol

(4) A M A Am J D Ch ld 88 732 739 Dec mb 1954

abrasion on the hand of a sheep butcher or some other direct contact with animal organic matter After two to seven days slight pain was felt around the inoculation site Itching throbbing burning and tingling ensued then stiffness around the adjacent joint and the finger became swollen The characteristic purplish rash appeared slowly First there was a small red spot sharply defined and slightly elevated as this faded the lesion extended peripherally progressing slowly to the back of the hand and often down the next finger never above the wrist The original area might be completely healed when a new area became purplish No fluctuation or pitting on pressure was present Involution occurred without desquamation or suppuration Fever to 99 6 F was present in about 10% with mild headache and malaise Average duration before penicillin was introduced was 7 days though one case lasted 45 days The disease is self limited but penicillin shortens its course

Diagnosis should not be missed if the apparent injury and site and the slowly progressive lesion with its characteristic spread and benign course are considered Absence of pus the color a normal leukocyte count location and slow progression differentiate the condition from true erysipelas which usually occurs on the face and scalp and is more acute

Recurrent Erysipeloid Cellulitis of Lower Extremities J F Hamilton[3] (Memphis) defines the disease as localized recurring cellulitis characterized by general malaise anorexia pain rigors fever swelling redness of one or the other of the lower limbs rarely both associated with signs of fungous infection of the feet and preceded by trauma recent or remote The etiologic factor is thought to be a fungus or a streptococcus antigen or both

Hamilton believes there can be no erysipeloid cellulitis which is not preceded by a break in the skin of the toes or feet due to fungous infection usually chronic Trauma in or near the site of the recurring attacks of cellulitis appears to be prerequisite even though it is not recalled by the patient and visible evidence of trauma may be lacking

Apparently there is a variable time interval or incubation period between manifestation of fungous infection on the feet and appearance of clinical symptoms and signs Onset

(3) South M J 47 778-783 August 1954

of penicillin in pneumococcic meningitis Why not take time to examine the purulent fluid by Gram stain? That together with an analysis of the circumstances under which infection developed may enable the physician to be somewhat more accurate in his antimicrobial therapy —Ed]

Salmonella Choleraesuis Clinical and Epidemiologic Evaluation of 329 Infections Identified between 1940 and 1954 in New York Salmonella Center is presented by Ivan Saphra and Michael Wassermann[5] Salmonella choleraesuis has appeared in the literature under the names Bacillus choleraesuis B suipestifer and S suipestifer European or Kunzendorf type and American type In the United States and adjoining areas practically only the European type is found Only one strain received at the Center was S typhisuis and 10 strains of S paratyphi C were indentified Since these caused clinical signs similar to those produced by S choleraesuis they were included in this study Approximately 90% of physicians returned satisfactory data when questionnaires were sent out for information about age sex source of isolation (feces blood etc) clinical history and epidemiologic correlation and 329 strains were available for evaluation

The high incidence (144 cases) of septicemia without local manifestations and with a high spiking fever is conspicuous In 19 other cases of septicemia there was a more continuous typhoid like fever with enlargement of spleen and occasional rose spots These figures are in marked contrast to all other salmonelloses except typhoid fever No positive stool cultures were found in these 163 cases In 43 cases focal manifestations took the form of abscesses and other inflammatory processes with 11 instances of osteomyelitis and 8 of osteoarthritis In 32 there were clinical features of pneumonia with positive sputum or blood cultures or both or of pleurisy or empyema with isolation of S choleraesuis from the exudate and occasionally from blood There were 10 cases of kidney infection and 7 of meningitis with isolation of the organism from urine and spinal fluid respectively In 10 cases of fatal subacute bacterial endocarditis organisms were isolated from blood or from the heart valves at necropsy There were only 53 cases of gastroenteritis 3 of them listed as ulcerative colitis Healthy carriers one of them a convalescent were encountered only three times

(5) Am J M S 228 525 533 Nov mbe 1954

chlortetracycline and oxytetracycline The six cases at Children s Hospital Los Angeles occurred over a 10 year period representing an incidence of 1 55 cases of purulent meningitis during that time

The oldest of the 16 patients was 13 months average age was 3 2 median 2 months Cultures of blood were positive in 10 of 13 cases confirming Bornstein s theory that meningitis is usually the result of septicemia Relatively high incidence of meningeal localization of this and other enteric organisms in newborns tends to substantiate the theory of a locus minoris resistentiae secondary to birth trauma

There were five fatalities and two recoveries with striking residuals one of which ultimately ended in death nine survived without complications Of those who died one received no therapy one died nine hours after admission and one received only sulfadiazine Of 13 who received at least two antimicrobial agents 9 recovered completely of 8 given at least one broad spectrum antibiotic 5 recovered completely

These results lead to the cautious statement that in a small group the newer antibiotics have favorably altered the course of salmonella meningitis The practice at Children s Hospital is to give all children with purulent cerebrospinal fluid at least four antimicrobial agents (sulfadiazine penicillin streptomycin and oxytetracycline) *until bacteriologic* diagnosis is made The drug or mode of administration may then be varied depending on the organism its sensitivity and the patient s response Once salmonella has been identified penicillin can be omitted and chloramphenicol added Since there is high frequency of relapse in this *form of meningitis* the patient should be maintained on at least one and preferably two wide spectrum antibiotics for several weeks after all signs have disappeared

Infection contracted during the first few days of life will respond favorably to therapy if diagnosed early Intrathecal medication appears of value in recalcitrant infections No one drug was of help in all cases

[Although therapy with combinations of antimicrobial agents is advantageous at times I am a little overwhelmed at the routine employment of sulfadiazine penicillin streptomycin and oxytetracycline in any child with purulent spinal fluid *Even this shotgun would not be best* for salmonella meningitis the disease under discussion And there is some clinical evidence that the tetracyclines interfere with the beneficial effect

two for 1 year The control group consisted of 21 patients treated with oxytetracycline and streptomycin for three weeks

Brucella melitensis was isolated from the blood in 43 (90%) of the patients from urine in 12 (25%) and from marrow in 12 (40% of the 30 patients so examined) The five bacteriologically negative cases were clinically indistinguishable from the positive reactors and had brucella agglutinations of 1 640 or 1 1280

Clinical response to therapy was rapid and dramatic Patients became afebrile in an average of 22 hours after institution of therapy compared to 4 6 days in the control group not receiving cortisone Exacerbations of fever or symptoms similar to the Herxheimer reaction were fewer (17%) than in the control group (55%) Although relapse rates appeared to be higher in patients receiving cortisone for one to three weeks (29 33%) than in those who received it up to four days (14 18%) the differences were not statistically significant Brucella agglutination titers appeared to be depressed by cortisone therapy

Occasional major side effects of cortisone militate against its general use in brucellosis The possible effects of lowering host resistance or causing more frequent relapses weigh against use of cortisone either alone or for long periods even with antibiotic therapy Its dramatic effect in alleviating toxemia however makes the discriminate use of cortisone a helpful adjunct during the first four or five days of specific antibiotic therapy of acute brucellosis

[In acutely ill persons the use of cortisone during the first three or four days of antibiotic therapy appears to be immediately beneficial and not unduly hazardous —Ed]

CHOLERA

Intravascular Hemolysis in Cholera Effect of Oxytetracycline S N De K P Sengupta and N N Chanda[7] (Nilratan Sircar Med College Calcutta) found hyperbilirubinemia in 30 patients with bacteriologically proved cholera In 23 treatment consisted of intravenous saline infusion 7 received oxytetracycline also Increased bilirubin in

(7) Lancet 1 807 809 Apr 17 1954

Salmonella choleraesuis infection predominated in males (2 1) whereas S oranienburg S typhimurium and S anatum had an approximately equal sex distribution Carrier rate of S choleraesuis was less than 1% while that of the other three ranged between 9 and 33% Mortality rate for S choleraesuis was 21% S oranienburg 4 7% S typhimurium 4% and S anatum 2% S choleraesuis was isolated from blood and other parenteral sources in a large number of cases and exclusively from feces in only 26 For all other types positive stool cultures were the rule

Incidence of S choleraesuis compared with other frequent salmonella types in 4 000 consecutive cases of human infection between 1939 and 1941 excluding S typhi cases and those from military sources was 7 2% representing the fifth place in frequency after S typhimurium S newport S oranienburg and S montevideo

The invasiveness and pathogenicity of S choleraesuis and S paratyphi C make them a clinical problem The high incidence of septicemia with or without focal manifestations and rarity of gastroenteritis in infections with these organisms put them into one category with S typhi and to a lesser degree with S paratyphi A and B They surpass all of the latter in their mortality rate

Epidemiologic evidence points to the hog as the main source of S choleraesuis infections although the ecologic prerequisite of the individual infection are obscure

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BRUCELLOSIS

Cortisone and Combined Antibiotic Therapy of Acute Brucellosis Melitensis Gordon B Magill John H Killough and Sami I Said[6] (U S Naval Research Unit Cairo) treated 48 patients with acute and subacute brucellosis with a combination of cortisone oxytetracycline and dihydrostreptomycin for three weeks Cases were selected on the basis of brucella agglutination of 1 160 or above in hospitalized patients with undiagnosed febrile illnesses Forty five patients had acute brucellosis with illness for 12 90 days one had the subacute variety with illness for 4 months and

(6) Am J Med. 16 810 816 Ju 1954

oval area of skin inflammation Although there was no evidence that the infection had spread from the thumb pasteurella infection was suspected and proved by intradermal reaction to antigen Antibiotic treatment was started immediately with a daily do e of 10 000 000 units of penicillin and 1 Gm streptomycin On the second day temperature fell to 100 4 F and the third to 99 5 F The general condition improved and pains and dysphagia disappeared Locally edema and redness rapidly regressed and only slight pain on palpation persisted The dermitis on the chest regressed more slowly and induration of the subcutaneous tissue which was extremely sensitive to pressure persisted for a long time

The authors believe that the unusual spreading of the cellulitis was due to the high toxicity of the pasteurella concerned Pasteurellae are sensitive to all antibiotic but in degrees which vary from strain to strain If the antibiotic selected to treat a pasteurella infection is effective its use should be prolonged sufficiently to avoid a relapse If it is ineffective another antibiotic should be given In patients treated tardily the infection is resistant to antibiotics and to sulfonamides and intradermal injection of antigen must be used

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NONSPECIFIC BACTERIAL INFECTIONS OF THE LUNGS

Suppurative Pneumonia in the Bantu Associated with Mixed Bacterial Flora Suppurative pneumonia was defined by Nichol on as an inflammatory consolidation of the lung which proceeds to suppuration A heterogeneous group of bacteria cause and maintain the suppuration In 260 cases of pneumonia observed at Pretoria General Hospital in adult Bantu patients L D Erasmus[9] found 36 of this type Males predominated 5 1 Age range was 14-80 with most patients aged 20-40 Onset was often insidious in 27 patients with lung abscess and acute in 8 of 9 without cavitation Physical signs in the chest were variable Clubbing of the fingers occurred in 14 patients with lung abscess and in 2 others Sputum was often blood streaked and varied in quantity from 2 to 16 oz in 24 hours Patients with abscess had an initial leukocyte count of 7 000 24 000 in those without cavitation total count was 6 000 35 000 Bronchoscopy showed

(9) B t. J T be 48 131 140 Ap 1 1954

the blood was ascribed to intravascular hemolysis induced by the hemolysin of Vibrio cholerae Controls without cholera but with diarrhea and comparable hemoconcentration did not show this change Maximal rise of serum bilirubin level on the 2d day its persistence on the 4th day when patients had recovered from shock and hemoconcentration and absence of prompt bilirubin in the serum made it unlikely that toxic or anoxic hepatic injury caused the rise No significant histologic changes were found in the livers of patients dying of cholera Occurrence of frank hemoglobinemia or hemoglobinuria or both in five patients (including one reported earlier) left no doubt as to the cause of hyperbilirubinemia and suggested that a relatively milder and slower hemolysis might explain the increased serum bilirubin level in the others

Prognosis in patients with hemoglobinemia with or without hemoglobinuria appears serious Three of the five patients died between the 8th and 10th day in postcholeric uremia one died in shock and one recovered Initial hemoglobinemia may be important in development of postcholeric uremia

Only 1 of 26 patients without hemoglobinemia died during this epidemic It was found incidentally that the patients not having sharp rise of serum bilirubin levels on the 2d day had received oxytetracycline suggesting that this antibiotic may have a definite beneficial effect on at least one perhaps ominous pathologic process in cholera

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PASTEURELLOSIS

Human Pasteurellosis Development of Scapulocervical Cellulitis after a Hand Wound In most cases of pasteurella infection of the hand inflammation develops around an animal bite or scratch Robert Worms and Yves Le Quintrec[8] (Paris) report an atypical case

Woman 53 cut her thumb on a broken dish from which a cat had eaten Several days later chills and fever (104 F) developed Intense pain and inflammation involved the entire shoulder to the cervical region and the cellular tissue of the superior mediastinum. On the right side of the chest at the level of the eighth rib was an

(8) Presse m d. 63 77 78 J n 22 1955

40-65 has fallen from 500 600 per million to 100 per million but there has been no comparable fall in death rate from bronchitis which has remained at 800 1 000 per million for the last 10 years Possible explanations are that (1) most patients with bronchitis do not receive antibiotics (2) chemical viral and bacterial causes of exacerbations of bronchitis are not susceptible to available drugs and (3) factors besides infection influence the prognosis of acute respiratory infections in bronchitic subjects E Keith Westlake[1] (Hammersmith Postgrad Hosp London) presents evidence for the third possibility in a study of 30 patients with severe respiratory infections hospitalized between December 1953 and April 1954

Six with lobar pneumonia had no previous history of chronic respiratory disease Twenty four had a long history of chronic bronchitis and were hospitalized with exacerbations of acute bronchitis bronchopneumonia or lobar pneumonia in 10 of these the respiratory infection had precipitated congestive heart failure Chronic bronchitis was diagnosed if there was a history of chronic cough and repeated episodes of winter bronchitis and chronic bronchitis with emphysema if there was also dyspnea on exertion (unrelated to bronchospasm) and the maximum breathing capacity was under 80 L /minute in males and 60 L in females A further diagnosis of cor pulmonale was made if on screening or at necropsy there was hypertrophy of the right ventricle

In the six patients without a previous history of respiratory disease arterial CO_2 tension was unchanged or was lower than the level on recovery This is the normal physiologic response to respiratory disease In 18 of 24 with bronchitis or emphysema the initial arterial CO tension was 5 32 mm higher than on recovery These patients may be said to have been in respiratory failure on hospitalization

Acute respiratory failure with increasing anoxemia hypercapnia and acidemia is responsible for the clinical picture observed during exacerbation of chronic bronchitic infection which includes headache raised intracranial pressure papilledema mental confusion hallucinations sweating myoclonic jerking increased cardiac output pulmonary hypertension and congestive cardiac failure

(1) Brit M J 2 1012 1018 Oct 30 1954

reddening of the mucosa of the bronchial orifice nearest the lesion and of adjacent mucosa in the main stem bronchus No inhaled foreign body bronchial stenosis or intrabronchial neoplasm was found

Sputum cultures showed a mixture of organisms often found in oral infections Signs of infection were present only in the gums and teeth—mostly extensive caries and massive tartar encrustations with swollen suppurating gums Incidence of dental caries or gingival sepsis or both in 36 patients with suppurative pneumonia was 83% compared with 18% in 200 patients of similar age with non suppurative pneumonia

The site of the lesion was similar with or without abscess The posterior segment of the upper lobe or apical segment of the lower lobe was involved in 30 cases in the right lung 15 times oftener than in the left It has been shown that iodized oil instilled into the trachea lodges in the posterior segment of the upper lobe with the subject on his side and in the apex of the lower lobe when he is on his back

Apart from bronchogenic spread and residual bronchiectasis the only serious complication was putrid empyema in two patients Lesions were attributed to rupture into the free pleural space of a small subpleural abscess with formation of tension pyopneumothorax Treatment included penicillin and other antibiotics chosen by sensitivity tests sulfadiazine postural drainage and bronchoscopy with aspiration All patients without cavitation recovered completely except one with residual bronchiectasis One patient with lung abscess died in two days

The type of bacterial flora and site of the lesion indicate that lung infection must have resulted from aspiration of infected material Dental neglect is so much commoner in the Bantu that results of dental sepsis are most easily demonstrated in this group but conclusions probably apply equally to others with dental sepsis

[The term "suppurative pneumonia" encountered in British medical writing more often than in American seems a good one We are all familiar with these cases in which sputum culture does not reveal a predominant pathogen the features are not those of a viral pneumonia and sometimes lung abscess develops The mode of infection postulated—"bronchial embolism" from areas of oral sepsis—seems reasonable —Ed.]

Respiratory Failure in Acute Chest Infections Since the introduction of chemotherapy in 1937 38 mortality in England and Wales from lobar pneumonia among men aged

the back and abdomen with spasm still prevailed Oxygen uptake studies were made using a Krogh apparatus and values expressed as percentages in excess of the calculated normal BMR (Fig 6) The first reading was 114% above normal BMR despite the fact that the most difficult stage of the disease had passed The values for oxygen uptake then fell parallel with clinical improvement Two weeks after onset he was relatively free from symptoms except for aches and some muscular hypertonicity which lasted until the third week Normal values were not recorded until four weeks after the onset of illness

The effect of avertin® on oxygen uptake was assessed on the sixth day Before drug therapy BMR was 97% above normal 45 minutes after avertin® it fell to 8% above normal

In treatment of tetanus apart from other measures special attention should be paid to factors concerned with increased metabolism (1) reduction of metabolic rate by administration of sedatives and neuromuscular blocking agents such as curare decamethonium and succinylcholine or interneuronal depressing drugs like mephenesin (2) provision of adequate oxygen and (3) provision of adequate calories

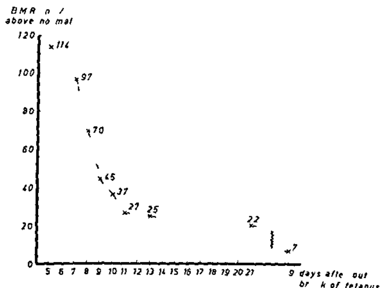
Tetanus in Heroin Addicts There have been many reports of malaria septicemia bacterial endocarditis and viral hepatitis in heroin addicts due to promiscuous use of needles and syringes but few of tetanus Abraham Levinson Robert L Marske and Max K Shein[3] (Cook County Hosp) found that 12 of 22 patients treated for tetanus in 20 months were heroin addicts Nine were women and 8 were aged 20-30 (60% of nonaddicts were over 40) all were Negroes

Symptoms differed from those in tetanus after burns or trauma In all but one patient pain or stiffness in the neck or back preceded onset of trismus by 12 24 hours Temperature rose to 103 105 F within 36 48 hours and coma appeared early usually in 12 36 hours after initial symptoms In nonaddicts the first symptom was trismus temperatures were consistently lower and coma did not occur except as a preterminal event in fatal cases

Mortality rate was 100% among addicts 40% among nonaddicts Intensive study is needed in treatment of tetanus in heroin addicts particularly with regard to withdrawal of heroin

(3) J A M A 157 658 660 Feb 19 1955

Metabolic Rate in Tetanus An adequate caloric intake in treatment of tetanus is important as the magnitude of metabolism during the course of the disease is considerable The amount of work done not only during the reflex spasms



F g 6—O yg n mpti n f m fifth d y f d e p s d in pe cent ge bove calc lated orm l BMR C r e shows d ea n m t b l c te wh h w pa allel to cl c l mp oveme t f t t n (C rte y f Holmdahl M H a d Tho en L A ta ch d v 107 335 340 1954)

but also during the intervals between because of the increased tone of the musculature varies Martin H Son Holmdahl and Lars Thoren[2] (Univ of Uppsala) report a case of tetanus in which it was possible to measure oxygen uptake

Man 54 had burns following electric shock Ten days later there was stiffness of the face and back muscles followed in a day by pronounced trismus and difficulty in speech Tetanus was diagnosed and appropriate therapy instituted Five days later there was considerable improvement but trismus and hypertonicity of the muscles of

(2) Acta ch r scand n 107 335 340 1954

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(3) J A M A 157 658 660 Feb 19 1955

Cortisone and Hydrocortisone Given Parenterally and Orally in Severe Tetanus Although tetanus is rarely encountered in temperate zones it remains common in tropical areas In India mortality varies between 46 and 56% Severity of tetanus can be estimated from the period of incubation time between injury and first symptom and time between first symptom and development of convulsions When incubation period is less than 7 days or period of onset less than 48 hours there is little chance of recovery

Recently Roger A Lewis Rajaninath S Satoskar Gopal krishna G Joag Bhalchandra T Dave and Jamnadas C Patel[4] (Seth G S Med College Bombay India) published a controlled study on severe cases of tetanus in which half the patients were given a continuous intravenous infusion of corticotropin in doses of about 20 mg a day In general the clinical course was milder and shorter when ACTH was given and reduction in mortality considerable but not of statistical significance In a subsequent study in which corticotropin and cortisone were given regulation of dosage was difficult but patients who received cortisone orally fared better than those who received injections

In the present study 20 control patients were alternated with 20 receiving hormone only those with the severest tetanus were selected for the series Five were given cortisone intramuscularly 10 cortisone by mouth and 5 hydrocortisone by mouth All had trismus convulsions fever and a short period of incubation or of onset (average 22 hours) Basic therapy included two intramuscular injections of 120 000 units of antitetanus serum daily injection of 400 000 units of penicillin intramuscular administration of paraldehyde and supportive measures Administration of cortisone was usually correlated with a drop in temperature and a fall in pulse and respiratory rate Fever often recurred when cortisone was reduced and in some cases did not respond to dosage used Cortisone given intramuscularly seemed to aggravate muscular spasms but cortisone or hydrocortisone orally resulted in a diminution in convulsions

Selection of severe cases appeared accurate since only 3 of 20 controls recovered whereas 46 of 56 patients excluded from the study survived None receiving cortisone injec

(4) J A M A 156 479-484 Oct 2 1954

tions recovered but 2 of 5 given hydrocortisone and 6 of 10 given cortisone by mouth recovered

Previous results suggesting that cortisone injections led to aggravation of convulsions were confirmed in this study with early death of the five patients given hormone injections The contrasting reduction in frequency and intensity of spasms in those who received hormone orally was striking even in cases in which slight fever persisted Results obtained with cortisone administered orally were statistically significant

[The authors have no good explanation for the apparent superiority of oral over parenteral administration of cortisone and one wonders whether this observation will be confirmed in a larger experience Certainly the lead deserves further study because we usually tend to avoid giving anything by mouth to patients with severe tetanus—Ed]

Fatal Tetanus in Boy after Prophylactic Tetanus Antitoxin A H M Littlewood A K Mant and G Payling Wright[5] record a case in which a patient contracted tetanus and died despite administration of the accepted prophylactic dose of antitoxin within two hours of injury Therapeutic failure was attributed to hypersensitivity to foreign serum proteins induced by a similar prophylactic injection given six months earlier

Boy 14 had lacerations of the fingers from an explosion He was given 1 500 I U antitetanus serum and penicillin without reaction Six months later he had similar injuries following another explosion He again received a course of penicillin and was given a prophylactic dose of 1 500 I U antitetanus serum after he failed to have reaction to a subcutaneous test dose Twelve days after the injury diagnosis of tetanus was made when he complained of difficulty in swallowing and showed trismus and stiffness of the erector spinae muscles He was desensitized by administration of 0 025 ml antitetanus serum subcutaneously the dose being doubled every 15 minutes until 1 ml had been given Then 1 ml was given intravenously and on injection of the first 0 1 ml considerable reaction was produced The skin of the face and neck became bright red pulse rate rose from 80 to 160/minute and respirations from 20 to 40/minute Tetanic spasms began the next day and increased in frequency and severity Despite tracheotomy and infusion of hyalase and succinycholine he died 5 days after appearance of symptoms and 17 days after injury

Autopsy revealed acute suppurative bronchopneumonia of the hydrostatic type acute fatty degeneration of the myocardium and liver and granulocytosis of the spleen No Clostridium tetani was found in cultures from the wounds

(5) B t M J 2 444 445 A g 21 1954

From studies on both human beings and animals there is evidence that previous administration of a soluble antigen including diphtheria and tetanus horse serum antitoxin leads to accelerated removal from the circulating blood on subsequent injection and consequently to curtailment of any effectiveness as a passive prophylactic agent It is thought that if a person has received an injection of any horse serum antitoxin irrespective of the disease for which it may have been given he should be promptly immunized against diphtheria and tetanus with the appropriate toxoid By thus creating the state of active immunity which can be effected without unpleasant side effects future need for passive protection against these diseases using horse serum antitoxin is unnecessary

[Hypersensitivity to horse serum may have contributed to failure of passive immunization to protect but an alternative explanation is simply that the conventional dose of 1 500 units just isn t enough See next article—Ed]

Prophylactic Failure of 1 500 Units of Tetanus Antitoxin Report of Two Cases is made by Mario Michael Martini[6] (Los Angeles County Hosp) since current literature and many textbooks still recommend 1 500 units of antitoxin as adequate prophylaxis

CASE 1 —Boy 16 had stiffness of the jaw four weeks after a toe was lacerated in a motorcycle accident The laceration had been sutured and penicillin and 1 500 units of tetanus antitoxin given Despite vigorous treatment he died during a generalized convulsion four days after hospitalization Clostridium tetanus was cultured from the wound

CASE 2 —Man 68 had severe deep lacerations of the left index and middle fingers from a buzz saw accident 11 days before onset of stiff neck difficulty in swallowing and jaw stiffness The lacerations had been sutured and 1 500 units of tetanus antitoxin given the day of injury He died the fourth hospital day Cultures of material from the gangrenous fingers showed Cl tetanus and Cl welchii

There have been 13 other reported cases in which prophylaxis with 1 500 units of antitoxin failed The 1 500 unit dose antedates World War I during the war it was found not wholly effective particularly in compound fractures and 10 000 unit doses were therefore given when a man was picked up on the battlefield at the sorting station and at the base hospital

For adequate passive immunization a dose of 10 000

(6) C l forn M d 8 189 191 M b 1955

rather than 1 500 units should be used This dosage is advocated by Spaeth and by Conn with dosage increased to 20 000 units if the wound is 24 hours old Bower holds that 30 000 units should be used In 1946 Spaeth made a plea apparently in vain that the time dishonored 1 500 unit vial be removed from stock

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LEPROSY

Leprosy Acquired in Military Service during World War II In 1947 Aycock in a study of leprosy in American veterans predicted that some cases would result from service in endemic regions during World War II Norman E Levan[7] (Bakersfield Calif) reports such a case Similar instances may be anticipated during the next 30 or more years in veterans of World War II and the Korean campaign

Man born in Kansas in 1907 while serving in the Philippines in July 1945 noticed a painless irregularly circular 2 in ulcer on the left calf The lesion healed spontaneously leaving a hypopigmented anesthetic atrophic scar During the next seven years the area of anesthesia slowly enlarged to involve most of the left calf After a painless burn in December 1952 at the site of the original ulcer he was seen by several physicians including a neurologist who suspected leprosy Extensive study revealed a positive histamine reaction and anhidrosis in the same area after injection of pilocarpine Lepromin test elicited no reaction and a diagnosis of leprosy was considered unconfirmed During the next two months areas of hyperesthesia appeared on the elbows and left concha

In June 1953 a few faint pink hypoesthetic macules with slightly thickened edges were noted on the chest back upper arms and thighs With the Fite stain rare acid fast bacilli were demonstrable Reaction to the lepromin test remained negative Diagnosis of leprosy of either early lepromatous or indeterminate type was established

Nothing in the patient s history indicated that the condition could have been contracted outside military service By arrangement with local and state health departments he was being treated with sulfoxone (diasone®) sodium as an outpatient He had to comply with several regulations for modified isolation to be lifted when 12 monthly skin scrapings for acid fast bacilli were negative Since treatment with sulfoxone the macules had completely disappeared and there had been no increase in anesthetic and hyperesthetic areas Acid fast bacilli ceased to be demonstrable within three months after beginning of treatment

(7) J A M A 156 126 127 Sept 11 1954

Disseminated Candidiasis A Schaberg J A Hildes and J C Wilt[8] report three cases observed at Winnipeg Municipal Hospitals within a year

CASE 1—Woman 22 had poliomyelitis three days before admission on Dec 14 1952 Penicillin 500 000 units and oxytetracycline 1 Gm were given parenterally each day and on December 22 streptomycin 1 Gm daily was started Early in January gross melena appeared and temperature rose to 105 F Death occurred January 9 Clinical diagnosis was acute bulbar poliomyelitis with gastrointestinal hemorrhage A blood culture three days before death showed Candida albicans Autopsy revealed acute poliomyelitis *involving* the cord medulla pons substantia nigra and hypothalamus and septicopyemia due to C albicans with localization in kidneys myocardium peripheral muscles and brain

CASE 2—Woman 49 first seen in July 1951 had advanced pulmonary tuberculosis which progressed slowly despite chemotherapy Severe hypogastric cramps beginning in May 1953 were thought *due to malignant or inflammatory obstruction or tuberculous entero*colitis Fluids intravenously and chlortetracycline produced temporary improvement but death occurred June 6 Autopsy showed extensive chronic bilateral pulmonary tuberculosis with cavitation chronic ulcerative colitis and generalized candidiasis with multiple abscesses in kidneys heart muscle and adrenals

CASE 3—Man 24 admitted Dec 17 1952 had typical acute poliomyelitis Sulfamethylthiadiazole 2 Gm penicillin G 500 000 units and oxytetracycline 750 mg were given daily for three weeks then streptomycin 1 Gm daily for nine days On Jan 8 1953 urinalysis revealed many bacteria and yeast cells later identified as C albicans Antibiotics were stopped and sulfathiazole was given in high dosage for five days without effect Undecylenic acid 15 Gm daily by mouth for six days was ineffective Cycloheximide 60 mg daily was given intramuscularly for over two months Three blood cultures during three months were sterile but C albicans was repeatedly isolated from catheter urine Pyuria was not affected by stilbamidine intravenously In June 1954 the patient still had severe residual paralysis but his general health was good and the chronic urinary tract infection was asymptomatic Diagnosis was extensive bulbospinal poliomyelitis complicated by C albicans septicemia resulting in chronic pyuria

Case 3 and one reported by Wessler and Browne are the only known cases in which the organism was isolated from the blood of patients living at the time of the report

The clinical importance of recovery of candida from

(8) A M A. Arch Int Med 95 112 117 J ry 1955

human material is still a problem In many cases of so called bronchopulmonary candidiasis and of diarrhea after intensive antibiotic therapy the actual importance of the fungus may be debated Reported cases of generalized candidiasis mycotic endocarditis and meningitis all occurred in patients in poor general state The authors patients were in extremely poor condition when their infection developed all had extensive antibiotic therapy and were maintained only on fluids parenterally for considerable time The relative importance of general debility as opposed to a specific effect of antibiotic therapy is difficult to assess

[Doubtless many factors may predispose to systemic fungous infections In recent years we have seen strong evidence that antibiotic therapy may be one In addition such disorders as diabetes mellitus the lymphomas and a state of general debility also seem to be associated —Ed.]

North American Blastomycosis Clinical Forms of Disease and Treatment with Stilbamidine and 2 Hydroxystilbamidine W D Sutliff J Warren Kyle and John L Hobson[9] (Memphis Tenn) present data on 25 cases to show that the aromatic diamidines stilbamidine and 2 hydroxystilbamidine are an improvement over therapy formerly used in the treatment of North American blastomycosis In all cases mycologic culture was necessary for recognition of the causative organism The lesions were chiefly cutaneous pulmonary and osteomyelitic Stilbamidine was administered intravenously in doses of 150 mg daily dissolved in 500 ml of 5% glucose in three courses of 10 days each with 1 2 week rest periods 2 Hydroxystilbamidine was administered intravenously in a daily dose of 225 mg dissolved in 500 ml of 5% glucose for 30 days, with repetition of the course if necessary

In 5 of 11 patients treated by various measures (including surgery and potassium iodide) before the aromatic diamidines were used the lesions were arrested for 16-59 months after therapy In three of the five the lesions were excised surgically Four patients were unimproved and were later treated with stilbamidine and two died of the active disease

In six of seven patients treated with stilbamidine the disease was arrested and remained so for 2 21 months after therapy In five the lesions were arrested in one to two months after beginning therapy One patient relapsed after

(9) A I t M d 41 89 107 J ly 1954

a symptom free period of 19 months Another patient in whom the disease was arrested died probably of coronary artery disease Stilbamidine was administered in amounts ranging from 1 65 to 8 2 Gm during periods of 10 days to 5 months In five patients trigeminal neuritis developed and was so severe in one that the drug was discontinued

The disease was arrested in 7 of 12 patients treated with 2 hydroxystilbamidine In three of these improvement has been maintained for 15 24 months In two patients the general condition improved but chronic pulmonary lesions persisted, and three patients were unimproved Of the latter two are refractory to therapy The drug was administered in amounts ranging from 2 to 45 2 Gm for 10 days to 13 months None of the patients had toxic neuritis but some had weakness

A relatively good prognosis was associated with solitary lesions or lesions confined to one organ system

Further precautions to avoid toxicity adjustment of dosage to avoid relapses or to cure refractory lesions and longer periods of observations are needed to define the optimal results from therapy with the aromatic diamidines

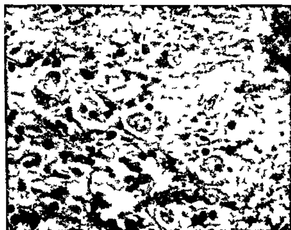
Torulosis Case Mimicking Hodgkin s Disease and Rodent Ulcer and Presumed Case of Pulmonary Torulosis with Acute Dissemination Two cases of disseminated mycotic infection are described by W St C Symmers[1] (Charing Cross Hosp London) One case masqueraded as Hodgkin s disease and pulmonary tuberculosis until Cryptococcus neoformans was found in lesions which simulated rodent ulcers Cryptococci were found on histologic re examination of lymph nodes excised when lymphadenopathy had appeared three years earlier Death was due to hemorrhage in an atypical cryptococcic granuloma of the brain

The second patient had pulmonary lesions which simulated abscesses but proved to be large caseous granulomas in which morphologically typical cryptococci were present True suppurative lesions the result of acute terminal dissemination of the infection and containing large numbers of the organisms were present in the spleen lymph nodes and liver These lesions have not previously been described in torulosis

(1) Lan t 1068 10 4 No 1 1953

Amebic Granuloma Report of Four Cases and Review of the Literature is presented by Charles G Spicknall and E Converse Peirce (U S P H S Hosp)

CASE 1—Man 33 was hospitalized because of right lower quadrant pain of six hours duration Diagnosis was acute appendicitis Exploration revealed a firm enlarged thickened and friable cecum Biopsy disclosed inflammatory reaction No amebas were seen but complement fixation for amebiasis was positive and he was treated



F g 7—B p y f ect 1 1 h w g E d m b h t lyt (C t y f Sp k ll C G d P E C N w E gl d J M d 50 1055 106 J 24 1954)

with emetine He was thought to present a typical picture of amebic involvement of the cecum masquerading as acute appendicitis

CASE 2—Man 66 was hospitalized because of sudden onset of diarrhea eight days earlier On rectal examination a fixed irregular firm tender annular lesion with a greatly narrowed lumen was felt Biopsy showed diffuse granulomatous reaction with many colonies of Endameba histolytica scattered through the tissue (Fig 7) Four days after institution of chlortetracycline therapy he was almost completely asymptomatic On re examination of the rectum the lesion was softer and less tender and the examining finger could be passed through the constriction This is an instance in which amebic granuloma of the rectum simulated carcinoma

( ) N w E gl d J M d 2 0 10 1062 J 4 1954

Case 3 —Man 49 was hospitalized complaining of diarrhea of three or four weeks duration Cysts of E histolytica were found *in a stool specimen Barium enema revealed distortion of the mucosal* pattern of the cecum with deformity of the tip Treatment for amebiasis was instituted with fumagillin One month later he was readmitted because of abdominal pain and diarrhea for three days Rectal examination revealed a painful annular mass which on biopsy showed inflammatory tissue with E histolytica present He was given oxytetracycline and chloroquine With improvement he was placed on diiodoquin and carbarsone *Forty six days after* treatment rectal mucosa was entirely normal

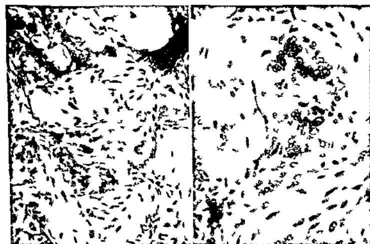
Case 4 —Man 38 was hospitalized because of right lower quadrant pain of 12 days duration On examination a tender well defined firm mass was felt Two stool specimens revealed many cysts of E histolytica Barium enema 11 days later showed a constant deformity of the tip and lateral wall of the cecum Two weeks later *the mass spontaneously disappeared but tenderness persisted until* after therapy with chloroquine and carbarsone was instituted

Amebic granulomas can simulate other inflammatory diseases or neoplasms of the colon Amebiasis and carcinoma of the colon can coexist When a lesion of the colon is inaccessible to biopsy except by laparotomy and an amebic granuloma is suspected therapeutic trial with antiamebic drugs should be instituted before surgery is performed Most lesions disappear completely with a month s treatment Surgery is dangerous in the presence of amebiasis or amebic granulomas and is indicated only for complications Prompt recognition of the disease at operation and proper therapy often prevent death

MEASLES

Propagation in Tissue Cultures of Cytopathogenic Agents from Patients with Measles John F Enders and Thomas C Peebles[3] *(Harvard Med School) attempted to cultivate* the agent of measles in cultures of human and monkey cells using procedures applied successfully to propagation of poliomyelitis viruses *In blood and throat washings of* typical cases of measles agents have been demonstrated that can be maintained in serial passage in tissue cultures and which induce *distinctive cytopathic changes in renal* epithelial cells These agents are presumed to represent the viral species responsible for measles

(3) Proc Soc Exper Biol & Med 86 277 286 J 1954



F g 8 (t p l ft) —O tg wth f m l h ma en l ll fi d d t ed. C t l f ht F g 9 11 H m t ylin ×110

F g 9 (t p ght) —P t f ll tg wth h w F gu 8 H m t yl os ×300

F g 10 (b tt m l ft) —O tg wth f h ma l c ll h w g g t ll f rm t on d n l h ges 20 d y ft n lat n w th ml blood f m p t t w th l cally d gu sed mea l H m t xyh ×110

F g 11 (b tt m ght) —P rt n f ll tg wth h w n F gu 10 H m t xy l -e ×300

(C rt y f E d J F d P bl T C P oc Soc E pe B l & *Med* 86 77 286 J n 1954)

Throat washings venous blood and feces were obtained from seven patients soon after clinical diagnosis of measles was established Antibiotics were added to all throat specimens Stationary cultures with trypsinized human and rhesus monkey kidney were used to isolate these agents and their serial passage Multiplication of the agents in vitro was accompanied by characteristic changes in the cells Primarily these changes consisted in formation of syncytial giant cells wherein the chromatin assumes a marginal position and is replaced centrally by an acidophilic substance of unknown nature (Figs 8 11) The cytopathogenic effect of at least one of the agents was inhibited by convalescent phase measles serums from other patients with measles Antigen appeared during cultivation in vitro of measles agents that reacted specifically in complement fixation tests with convalescent phase measles serums

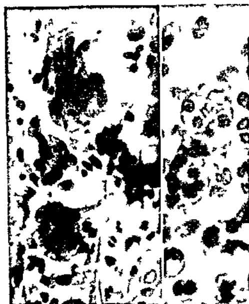
Although the emergence of antibodies during measles capable of suppressing the cytopathogenic effect and of fixing complement in the presence of infected tissue culture fluids afforded further evidence for the close association of these agents with measles two experiments essential in the establishment of the definitive etiologic role of this group of agents in measles remain to be carried out It will be necessary to produce measles in the monkey and in man with tissue culture materials after a number of passages in vitro sufficient to eliminate any virus introduced in the original inoculum Recovery of the virus from the experimental disease in these hosts should then be possible

[Dr Enders has made another important contribution isolation and cultivation of an agent which is almost certainly the virus of measles —Ed]

Characteristic Cell in Nasal Secretions during Prodromal Measles is described by Victor Tompkins and John C Macaulay[4] (Albany N Y) The multinucleate giant cell of lymphoid tissue (Warthin Finkeldey) is a well known finding in prodromal measles but epithelial giant cells of the bronchial mucosa are less well known A patient with a fatal case had an abundance of such epithelial giant cells and in the bronchial lumen shed forms were abundant The likelihood that sputum might contain the cells in prodromal measles was confirmed in a specimen taken some 48 hours

(4) J A M A 157 711 Feb 26 1955

before exanthem in a living patient Since suptum specimens are difficult to obtain from children the cells were sought in nasal secretions and were demonstrated regularly in 10 patients in different stages of illness ranging from the fifth prodromal day to the day of exanthem Control preparations from patients with upper respiratory tract infections



F g 12 (l ft) —F sed p t y p th l m ×460
F g 13 (ght) —M lt u l te ll w th n l d sely ta ed nd h unken ×960
(Cou t y f T mpk V d M lay J C J A M A 57 711 F b 26 1955)

allergic states rashes roseola and rubella failed to show comparable structures

Glairy mucus was aspirated from the nose well up in the turbinate region and spread liberally and gently on a glass slide Preparations were fixed immediately in an alcohol-ether mixture and stained by the Papanicolaou technic Wright stained air dried films also proved satisfactory

In the earliest cases the large multinucleate cells were basophilic with well preserved nuclei resembling fused

normal respiratory epithelium (Fig 12) Occasional syncytial clumps preserved a brush border with cilia or large vacuoles presumably those of the mucus secreting goblet cells Later the cytoplasm became profoundly eosinophile or orangophile with nuclei that tended to be densely stained and shrunken (Fig 13) Such cells occasionally contained brightly acidophilic discrete cytoplasmic inclusions

Usefulness and reliability of this simple examination can be determined only by more general use

[Conceivably this procedure may have practical value as an aid to early recognition of measles The technic is simple enough to make it generally available —Ed]

RUBELLA

Rubella Virus in Tissue Culture S G Anderson[5] (Melbourne Univ Australia) reports results indicating that rubella virus can multiply and produce lesions in tissue cultures of monkey kidney and human embryo Throat washing from a patient with rubella was used to inoculate cultures of monkey kidney Five days after inoculation of the fifth passage multinucleate areas increased 11 days after inoculation each tube carried 15 100 multinucleate areas per sheet of outgrowth and large mononucleate cells were considerably increased Cytoplasm of both cell types frequently appeared abnormal presenting a structureless smeared appearance Nothing suggesting an intranuclear inclusion was seen and all nucleoli stained normally These abnormalities persisted through the ninth (present) passage

Other experiments indicated that the transmissible agent in the cultures was inactivated by convalescent serum but not by preinfection serum from the same person In a single experiment the virus was not inactivated by undiluted con valescent serum from a patient who had recently suffered a typical attack of measles

The only questionable features were resemblance of the lesions to those in cultures of measles virus in similar tissues and presence of a few multinucleate areas in control cul tures Evidence suggests that the patient from whom the original virus was obtained and the volunteer who provided two samples of serum (before and after experimental infec

(5) Lancet 2 1107 1108 N 27 1954

tion) had typical rubella Although the few multinucleate areas in control tubes could not be differentiated from the numerous areas characteristic of infected monkey kidney cultures limited experience with human embryo tissue showed complete absence of multinucleate cells in control cultures Hence this tissue may prove the most suitable for future work Excepting the possibility of unrecognized technical or logical fallacy in these initial experiments Anderson believes that they establish a case for growth of rubella virus in tissue culture

[Several others have attempted to isolate the agent of rubella in tissue culture and have not been successful The information presented in this preliminary communication does not add up to as convincing a case as Enders and Peebles report (this YEAR BOOK p 54) on probable cultivation of the virus of measles—Ed]

Soreness of Gums in Rubella Rubella has been referred to as a creature of many moods because of its resemblance to certain aspects of rubeola scarlet fever and infectious mononucleosis Now that the relation between rubella in early pregnancy and occurrence of congenital anomalies is well established the precise diagnosis in pregnant women or in persons to whom they may have been exposed has urgent implications Attention is called by Bruce L Brown[6] (Warren O) to soreness of the gums as a symptom of rubella which may be of value in establishing the diagnosis In about a third of several hundred patients the symptom usually appeared with onset of the exanthem and continued for a day or two Examination of the gums and teeth occasionally showed a slight gingival inflammation This soreness of the gums mentioned by a few writers has been suggested to be a feature of only some moods of the disease When present the symptom has been helpful in differentiating rubella from infectious mononucleosis and rubeola

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RABIES

Human Rabies Report of Three Cases diagnosed at autopsy is presented by Ethel E Erickson Peter M Marcuse and Bela Halpert[7] (Baylor Univ) Two men 29 and

(6) New England J Med 250 726 727 Ap 29 1954
(7) J A M A 155 8 3 825 J 26 1954

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37 and a woman 43 presented bizarre symptoms suggesting central nervous system involvement diagnosis of rabies was not made clinically Autopsy revealed the pathognomonic Negri bodies in brain tissue and in each instance subsequent inquiry disclosed that the patient had had direct contact with a suspected rabid dog or had been bitten by a rabid dog The incubation periods were 40 30 and 62 days but the fatal illness itself lasted only 6-9 days Two patients died on the third day in the hospital and one died the day after admission

Symptoms began *in each case* with localized pain which soon radiated to a much wider area cramps and paresthesias tremor and inability to swallow Fever and leukocytosis were present along with anxiety hysteria hyperexcitement and bizarre behavior In the two men leukocyte counts were 28 100 and 35 600 Irrationality and delirium progressed and there were signs of marked pulmonary congestion and consolidation In the terminal phase blood pressures were very low (86/64 80/? 94/50 respectively on admission) Administration of oxygen fluids parenterally antibiotics and pressor drugs had no apparent influence on the rapid deterioration

In communities where rabies in animals is prevalent rabies should be considered a possible cause of illness when a patient presents obscure severe nonlocalized central nervous system manifestations that culminate in death Whenever there is suspicion that a patient has had rabies a search should be made for the characteristic lesions in the brain at autopsy so that the disease may be identified The recorded increased incidence of human rabies in a community focuses attention on its source and leads to enforcement of laws and regulations This in turn decreases rabies in animals and reduces the chances of transmission *to other animals and to man*

Human Rabies Caused by Bat Bite In *1925* a paralytic disease of livestock near Port of Spain Trinidad killed several thousand animals During the epidemic traced to the bite of the vampire bat 55 human cases of rabies were reported Later epidemics affecting livestock proved to be rabies and traced to vampire bats occurred in western Mexico Honduras and Venezuela but no cases were re

ported in human beings The first human case of rabies resulting from bat bite in the United States is reported by S Edward Sulkin and Marion J Greve[8] (Univ of Texas)

Woman 43 was hospitalized for a febrile illness which had begun 16 days after she had stopped to investigate what was apparently a dead bat on the roadside The animal was not dead and bit her on the left forearm Illness began with aching in the left arm and a temperature of 103 F the next day nausea vomiting generalized aching and paralysis of the left arm appeared Inability to swallow led to lumbar puncture which revealed a total cell count of 24 Presumptive diagnosis was bulbar poliomyelitis although possibility of rabies could not be excluded She remained comatose and did not attempt to speak throughout her hospital stay On the fourth day blood pressure slowly fell to the unobtainable level and death occurred about three hours later

Postmortem pathologic diagnosis was encephalomyelitis with demonstrable Negri bodies in central motor neurons compatible with rabies

The extent of rabies in bats in certain areas of the United States should be explored thoroughly to establish the significance of the bat in the ecology of this disease

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MUMPS ORCHITIS

Mumps Cause of Infertility I Present Considerations John W Ballew and William H Masters[9] (Washington Univ) studied 79 infertile couple to learn the possible significance of previous mumps infection Nineteen men had had mumps orchitis (25%) and 11 of the 19 had azoospermia on repeated examinations

Regarding testicular involvement by the mumps virus one opinion is that although atrophic changes may occur in the affected tissue sterility is not a major residual factor The other with far fewer proponents is that mumps orchitis can cause significant infertility After their detailed inquiry the authors have concluded that mumps orchitis causing sterility or marked infertility in the male is a very real possibility Some believe that unilateral involvement does not materially affect procreative ability but in six cases of this type the sperm count was so low that sterility was almost inevitable

Mumps orchitis as a cause of infertility must be given

(8) T J M d 50 6 0 621 Augu t 1954
(9) F rt l & St 1 5 536 543 N Dec 1954

wider consideration Although the testicular inflammation may abate with little discernible harm it may in other cases irreparably damage procreative power In premarital counselling the time following the orchitis and the actual semen analysis should be stressed Reliable estimate of semen quality cannot be made by manual palpation of the testes or prostate Sometimes 10 years may elapse after the acute infection before the ultimate result of mumps orchitis may be satisfactorily evaluated

Effect of Corticotropin in Orchitis of Mumps Preliminary Report on six cases is presented by Jan H Solem[1] (Drammen Norway) Testicular involvement was severe in all patients who were unmarried men 18 29 previously healthy Four represented sporadic cases two were chosen from among over 20 patients with epidemic mumps

CASE 1 —Man 20 had bilateral parotid swelling four days before inflammation of right testis began with a chill fever (104 7 F) joint pains and a dragging sensation in the right groin Maximal enlargement of right scrotal sac and testis occurred three days later appearance was that of a large hydrocele and it was severely painful He was given 100 I U long acting corticotropin Two hours later tenderness of the testis had diminished by evening swelling had subsided and pain decreased Subsequent recovery was uneventful

CASE 2 —Man 18 had left sided orchitis on the fifth day after onset of parotitis Testis swelled to the size of a small orange with pain and inflammation There was also complicating pancreatitis On the fourth day after onset of orchitis 100 I U ACTH was given intramuscularly Swelling scrotal tenderness and pain subsided within 24 hours Symptoms recurred after 36 hours and response to a second injection was prompt and lasting Symptoms of pancreatitis also subsided

Three additional patients were treated successfully with a single injection of 100 I U ACTH with courses identical to that in Case 1

CASE 6 —Man 29 had bilateral parotitis complicated by bilateral orchitis which appeared the fourth day Immediate drop in temperature and increased sense of well being occurred after injection of 100 I U long acting ACTH left testis also improved promptly A definite relapse developed with fever and increasing right sided scrotal swelling and pain Another dose of ACTH was followed by some pain relief but temperature increased and swelling and inflammation did not improve until a third 100 unit dose of ACTH was given the following day Effect of ACTH was difficult to evaluate in this case probably more continuous hormone therapy from the beginning would have been better

(1) Acta med scand 149 341 344 1954

If the inflammation and exudation of mumps orchitis can be blocked by ACTH disturbance of spermatogenesis may possibly be prevented though this remains to be proved

[Our experience with ACTH and cortisone in mumps orchitis has been similar namely prompt and gratifying response in four of six cases We believe this therapy should be employed routinely as a symptomatic measure but whether it will diminish the incidence of subsequent atrophy and sterility remains to be determined —Ed]

INFECTIOUS MONONUCLEOSIS

Transmission of Infectious Mononucleosis Robert J Hoagland[2] (M C U S A) states that little is known about the communicability of this disease Attempts to transmit mononucleosis to animals and man have almost always been unsuccessful and there is no evidence pointing to food or water or insects as transmitting agents Reports of epidemics before discovery of the heterophile antibody reaction are undependable

Mononucleosis is most prevalent in the age group 17 25 and is rare in children and after age 40 The disease reported in children is usually an acute febrile illness clinically resembling mononucleosis but differing serologically and often hematologically The high incidence reported among college students and in the armed forces was corroborated by Hoagland s six years observation of cases among students at the U S Military Academy More cases were found in February and August than in other months However the disease was never seen in roommates an observation in accord with several investigations of college student populations The remarkable predilection for a narrow age span should have provided a clue to transmission and the hypothesis is proposed that mononucleosis is transmitted chiefly by intimate oral contact which allows for salivary exchange

Of 73 students with mononucleosis 71 gave a history of oral contact 32-49 days before onset of symptoms and 1 stated that he frequently drank soft drinks from bottles shared by others Transmission by sexual relations could definitely be ruled out A long incubation period would explain the high incidence in February and August which

(2) Am J M S 229 262 27 M h 1955

wider consideration Although the testicular inflammation may abate with little discernible harm it may in other cases irreparably damage procreative power In premarital counselling the time following the orchitis and the actual semen analysis should be stressed Reliable estimate of semen quality cannot be made by manual palpation of the testes or prostate Sometimes 10 years may elapse after the acute infection before the ultimate result of mumps orchitis may be satisfactorily evaluated

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(1) Acta med. scand nav 149 341 344 1954

severe that even with transient relief by narcotics swallowing became impossible Electrocardiogram showed increasing abnormal T wave inversion in precordial leads V V and V When oxytetracycline was discontinued after 7 Gm had been given he appeared to be prostrate Administration of corticotropin was begun on the 14th hospital day 25 mg in 1 000 ml of 5% glucose in water was given by intravenous drip over 10 hours and was repeated the following day Subsequently daily doses were reduced by 5 mg and terminated after six days when 100 mg corticotropin had been given His temperature dropped to normal on the first day of corticotropin therapy and remained so thereafter By the end of the second day clinical improvement was striking He became progressively more alert pharyngeal edema and lymphadenopathy subsided and heart sounds and ECG returned to normal A ravenous appetite developed and there was rapid gain in strength and weight

Although the incidence of spontaneous remission in infectious mononucleosis makes it difficult to evaluate the effect of any treatment the dramatic improvement in this case clinically and systemically strongly suggested that corticotropin had a beneficial effect Rapid and complete convalescence without sequelae was contrary to what might have been anticipated in so severe a case

[My impression i the same I have seen striking improvement in the throat inflammation and glandular tenderne s within 12 18 hours after administration of cortisone or ACTH I believe it is relatively safe and can be used as symptomatic treatment in severe cases —Ed]

OTHER VIRUS DISEASES

Clinical Observations on Smallpox and Complications of Smallpox Vaccination Their Prevention and Treatment are discussed on the basis of a study made in India for the World Health Organization by C Henry Kempe[4] (Univ of California) Smallpox remains one of the chief killers among virus diseases Over 400 000 cases occur each year the majority in Southeast Asia and Africa Mortality rate is never lower than 33% and especially in young children and in the aged frequently exceeds 60% There is no specific therapy and neither the wide spectrum antibiotics nor penicillin does more than prevent purulent complications

Contrary to general view smallpox does occur in persons successfully vaccinated In nonendemic regions protection is considered to last as long as 10 years but in endemic areas

(4) K F d M B ll 2 37 241 S pt O t 1954

followed by about 45 days the semiannual vacations with their maximal opportunities for contact during the academic year the students were generally confined to quarters An incubation period of about 40 days is supported by three cases reported in seamen who had been aboard ship for five weeks before onset of symptoms

The hypothesis of intimate oral transmission explains many observations absence of transmission in roommates failure of experimental transmission (presumably the agent does not survive outside the human body) rarity of serologically proved cases in children precise age group 17 26 and infrequent occurrence in married persons who are less likely to kiss promiscuously and in persons over 40 In over 200 cases observed since 1946 Hoagland found few in persons over 30 or in children under 14 The lack of cross infection on hospital wards despite the relative frequency of mononucleosis among young hospital personnel is also explained

[What a pity!—Ed]

Infectious Mononucleosis Treatment with Corticotropin in a severe case is reported by Robert L Brutsche and Charles F Naegele[3] (U S P H S Hosp San Francisco) This disease is usually benign and self limited producing asthenia for three to six weeks and subsiding without sequelae but in a few cases it causes severe and prolonged illness and sometimes death Course and duration are not changed by use of penicillin chlortetracycline or chloramphenicol

Man 21 was ill for four days with a sore neck generalized aching particularly in the back and joints severe frontal and occipital headache anorexia malaise chills and fever Temperature on hospitalization was 104 F and during the next four days ranged from 99 to 105 F daily Although the spiking temperature declined somewhat (100 102 F) increasing malaise and progressive sore throat were noted with pronounced pharyngeal hyperemia and extensive edema involving the uvula and soft palate Repeated throat cultures showed only normal flora On the fifth hospital day leukocytes numbered 7 900/cu mm with 66% lymphocytes of which 2% were abnormal A few days later heterophil antibody titer was 1 7168 with a titer of 1 224 after absorption with guinea pig kidney and 1 3 5 after beef erythrocyte absorption Despite oxytetracycline 500 mg by mouth every six hours and intensive supportive therapy his condition appeared to deteriorate Pharyngeal pain became so

(3) California Med 80 408-411 May 1954

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(4) K se F d M B ll 2 37 41 S pt O t 1954

successful yearly vaccination is required Over 80% of smallpox patients seen had been successfully vaccinated at least once but none within the preceding 12 months Although it is believed that vaccination performed promptly after exposure prevents smallpox incidence under these conditions varies between 10 and 40% For solid protection vaccination must be successfully performed before exposure Throughout Asia three or four simultaneous vaccinations are usually performed for primary vaccination while in some districts two or only one insertion is made In 2000 consecutive cases of smallpox in Madras there were 13 times as many cases in children having one primary vaccination scar as in those having four and five times as many in those with one scar as in those with two There appears also to be a definite correlation between size and severity of single vaccination insertions and resulting neutralizing antibody level and its duration

The clinical course of smallpox is characterized by explosive onset of high fever with severe headache backache and general malaise There is no rash All symptoms persist until usually on the third or fourth day the temperature abruptly drops and the patient feels much better The maculopapular eruption appears and becomes vesicular during the subsequent 24 hours Vesicles are most marked on face forearms and legs Distribution is typically centrifugal whereas that of chicken pox is centripetal On the fifth or sixth day the vesicles develop into pustules in which purulent bacteria become prominent in severely infected areas temperature frequently rises and toxicity increases Scabbing begins on the ninth or tenth day and usually has entirely disappeared 30 days after onset The patient is not considered noninfectious until the last scab has fallen The pustular phase may go directly into a septic phase in which pyogenic bacteria seed from the skin into the blood stream and thence to lungs bones joints etc Purulent complications in these and other organs and eventual death may occur if no antibiotic is given

Improvement in mortality rates will not be spectacular until a specific antibiotic is found In the meantime good medical and nursing care makes a remarkable difference in results Because of dysphagia due to lesions in the mouth

and throat fluid intake is usually poor and parenteral medication is required Use of a plastic stomach tube and feeding of boiled skim milk with a carbohydrate supplement around the clock is excellent treatment during the first 10 days Penicillin has decreased purulent complications during the pustular phase

In the United States a number of children die every year of serious complications of smallpox vaccination and there are many milder complications which are self limited and do not result in permanent disability Erythema multiforme is a generalized eruption occurring usually at the height of primary vaccination treatment consists in use of antihistamine drugs and reassurance Satellite lesions commonly occur around the primary vaccination site or in areas of the body to which they are carried by the child s or mother s hands Eczema vaccinatum characterized by vaccinia lesions over normal and diseased skin causes the largest number of deaths The source of virus in children with eczema is usually a sibling who has been vaccinated Mortality in severe cases is frequently as high as 40% despite energetic therapy Generalized vaccinia is caused by the presence of the vaccinia virus in the blood (viremia) from the site of primary vaccination take to all areas of the body resulting in satellite lesions over the skin An extremely rare and up to now universally fatal complication (at least four cases occurred during the past year in the U S) is vaccinia necrosum caused by complete inability to produce antibodies against the vaccinia virus Recent studies suggest that this may be related to absence or deficiency of gamma globulin and one child was successfully treated with large amounts of vaccinia immune gamma globulin

Distribution of Colorado Tick Fever and Virus Carrying Ticks The typical clinical picture of Colorado tick fever the only tick transmitted virus disease of man recognized in the Western Hemisphere is as follows Four to five days after exposure to ticks there is sudden onset of a chilly sensation severe headache nausea and occasionally vomiting Fever headache lumbar pains aching in the extremities and anorexia continue about two days A remission of about equal duration is followed by a relapse of two to three days Leukopenia with a count of 2 000 3 000 appears to be constant

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Improvement in mortality rates will not be spectacular until a specific antibiotic is found In the meantime good medical and nursing care makes a remarkable difference in results Because of dysphagia due to lesions in the mouth

stage from spinal fluid and serologic evidence showed that it had caused the aseptic meningitis

In the 11 patients aged 14 26 onset of illness was sudden (12 24 hours) with headache stiff neck backache myalgia low grade fever and malaise Two each complained of nausea and vomiting diffuse chest pain rhinitis and sore throat All showed clinical evidence of meningeal involvement and had inflammatory signs of serous meningitis in the cerebrospinal fluid Nuchal and spinal rigidity Kernig s and Brudzinski s sign and pleocytosis were seen in all cases Cerebrospinal fluid cell counts ranged from 22 to 99 cells/cu mm with a predominance of lymphocytes Myalgia diffuse in three patients and focal in the others involved symmetrical large muscle groups Fever was present for 3 5 days in nine patients and for 10 in the other two Symptoms lasted 6-9 days in eight and 10 15 in three Two relapses occurred after five and seven days Complete medical survey five months after recovery showed no sequelae

Fecal and blood specimens and throat swabs were collected from eight patients and cerebrospinal fluid specimens from four of these These materials were inoculated intraperitoneally into day old suckling mice because mice this age are most sensitive to group B viruses Symptoms of infection in the mice ranged from extreme weakness and ataxia to paralysis Coxsackie virus was isolated from six of the eight patients In four a virus was recovered from the stool only and in one each from a throat swab and a cerebrospinal fluid specimen only All isolated viruses were identified by neutralization tests as belonging to group B type 2 (Ohio)

Findings were surprisingly uniform considering the many variations encountered in an infection with Coxsackie viruses but the evidence proves that group B viruses commonly associated with pleurodynia can invade the central nervous system and cause benign meningitis clinically indistinguishable from serous meningitides caused by other infectious agents

[There had been some debate about the validity of previous reports of meningitis caused by Coxsackie viruses However evidence continues to accumulate favoring the view expressed here —Ed]

Controlled Study of Effect of Oral Penicillin G in Treatment of Nonspecific Upper Respiratory Infections was

Studies by Carl M Eklund Glen M Kohls and James M Brennan[5] (U S P H S Hamilton Mont) indicate that Colorado tick fever is not always so relatively benign Virus was isolated from the blood of five children with evidence of central nervous system involvement Encephalitis was suspected in four and meningitis in the fifth For a two year period beginning in 1952 examinations of blood from patients with a history of tick exposure regardless of the diagnosis of the attending physician yielded positive findings of virus in 193 patients exposed in California Colorado Idaho Montana Nevada Oregon Utah Washington and Wyoming 86 of these isolations were in the first seven months of 1954 All persons were exposed to ticks in the known distribution of Dermacentor andersoni the only species incriminated in transmission of the disease

Popularity of the known endemic area as a vacation land speed of modern transportation and incubation period of the disease make possible the appearance of Colorado tick fever in any part of the United States or elsewhere

Aseptic Meningitis Caused by Coxsackie Virus with Isolation of Virus from Cerebrospinal Fluid The numerous strains of Coxsackie viruses are grouped together mainly because they produce characteristic lesions in suckling mice or hamsters They are further segregated into A and B groups according to distinct pathologic changes they produce in suckling mice Group A viruses produce typical lesions in striated muscle resembling Zenker's hyaline degeneration and hardly any other recognizable pathologic changes Group B viruses produce only moderate muscle lesions but cause characteristic encephalopathy and panniculitis and in adult mice extensive pancreatitis There is strong evidence that in man group A strains cause herpangina and group B strains epidemic pleurodynia (Bornholm disease)

Klaus Hummeler Daniel Kirk and Mykola Ostapiuk[6] report an outbreak of infection with Coxsackie virus in an institution for mental defectives with patients showing clinical involvement of the central nervous system From one patient a Coxsackie virus was isolated during the acute

(5) J A M A 157 335 337 Jan 22 1955
(6) Ibid 156 676-679 Oct 16 1954

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made by G A Cronk D E Naumann K McDermott P Menter and M B Swift[7] (Syracuse Univ) All medications used were commercially prepared and identical in appearance In the controlled study 62 hospitalized patients with nonspecific upper respiratory infections were treated with (1) aspirin compound alone (2) aspirin compound with an antihistamine and (3) aspirin compound antihistamine and oral penicillin G The average hospitalization of the first two groups was 3 56 days and for the third group, 3 48 days The subjective responses objective findings and febrile course of the disease for these three groups were essentially the same

The marked reduction in mortality and morbidity from diseases susceptible to the readily available chemotherapeutic agents and antibiotics has been broadly publicized in both the medical and lay literature Under the influence of social economic and other ill defined forces, these agents have found common use in many self limited and relatively harmless diseases The trend continues in the absence of proved therapeutic benefits and in the presence of increasing reports of serious toxic reactions

[Once again we are shown that antibiotics have no value in the treatment of common respiratory disease—Ed]

NEW (?) DISEASES

Pharyngoconjunctival Fever Epidemiologic Studies of Recently Recognized Disease Entity Joseph A Bell Wallace P Rowe Joseph I Engler Robert H Parrott and Robert J Heubner[8] (Nat'l Inst of Health) observed over 300 cases of an acute respiratory illness spread from person to person which appears to represent a newly recognized communicable disease entity A newly discovered virus adenoidal pharyngeal conjunctival type 3 (APC-3) was recovered from 80 patients

The disease occurred in localized epidemic and in sporadic form in all age groups but predominantly in children It seemed more prevalent in summer and swimming pools and wading facilities were a suspected but unproved source of

(7) Am J Med 16 804-809 June 1954
(8) J A M A 157 1083 1092 Mar 6 1955

infection The illness was characterized by fever pharyngitis and conjunctivitis singly or in combination Temperature often rose to 103 or 104 F for a few days and lasted 1 10 days (average 4 6) subsiding by lysis The sore throat was generally mild examination usually showing the posterior oral pharynx injected and prominently studded with glary lymph follicles Nontender submaxillary lymphadenopathy was common Conjunctivitis of nonpurulent follicular type often monocular usually lasted one to three weeks There were no deaths and no sequelae were recognized

Differential diagnosis should consider leptospirosis influenza herpangina and various nonpurulent conjunctivitides Although there were fever headache nonpurulent conjunctivitis and a possible association with swimming pools the study patients did not have severe malaise muscle bone and joint ache vomiting stiff neck or the jaundice often seen in leptospirosis In influenza muscle joint and retro orbital pain is common and conjunctivitis not seen Also influenza outbreaks are rare in summer months Herpangina although common in the summer has characteristic lesions on palate and anterior pillars that differentiate it Neither epidemic keratoconjunctivitis nor inclusion conjunctivitis are commonly associated with general symptoms or have the short duration of the study cases

The APC viruses are viruses of the respiratory tract they produce unique cytopathic changes in tissue culture of epithelial cells The APC 3 virus was i olated from patients in each of the epidemic and sporadic outbreaks studied It was shown to invade the body tissues of the infected persons and was present almost exclusively during acute illness rarely being found before onset or after recovery The incubation period of the disease was found to be 5 9 days and the period of communicability indicated by the presence of virus was 10 days It is suggested that the disease entity be named pharyngoconjunctival fever

[A dividend of the discovery of a group of viruses recoverable from human adenoid tissue (see the 1954 55 YEAR BOOK p 75) This is probably not a new disease but one which would be difficult to distinguish as an entity without the aid of a spec fic laboratory test If one can remember the name one can keep the es ential clin cal features in m nd —Ed]

Clinical and Epidemiologic Features of Unusual Epidemic Exanthem In the ummer of 1951 inquiry of Massachu

setts physicians disclosed that an outbreak of a mild disease was fairly widespread and that its clinical features did not readily conform to those of commonly recognized exanthems Franklin A Neva Roy F Feemster and Ilse J Gorbach[9] (Boston) studied 18 patients, isolated certain transferable agents probably etiologically related to the disease and obtained additional data from questionnaires sent to 123 physicians

The 18 patients were aged from 4 months to 26 years, 2 were under a year 10 were 2-4 and all but the 3 adults were under 8 Only 5 including 1 adult were males The commonest finding was temperature elevation to about 102 F lasting only one or two days All children but only one adult exhibited varying skin eruption the adult having 8 or 10 barely noticeable pink maculopapular discrete lesions The lesions were generally pink or salmon slightly raised discrete and lighter than typical measles rash The rash, usually most evident on the face and upper chest, was also frequently observed on arms buttocks and legs Some patients had lesions of the soft palate and tonsils comparable with those described in herpangina No gingival or mucocutaneous lesions resembling herpes simplex were noted

Hospitalization was not necessary In several patients the skin eruption was almost the only sign of the disease Some children although febrile remained active and revealed no other signs of illness

After earlier attempts to isolate an agent from the patients failed materials were inoculated into flask cultures of human kidney tissue of the type used by Robbins and others for isolation of poliomyelitis virus From stool specimens of *seven patients transferable agents were isolated* Paired serums from 9 of 11 patients exhibited significant rise in titer of neutralizing antibody to at least one of the seven strains of cytopathogenic agents isolated

There is little doubt that the outbreak represents an infectious and communicable disease entity Whether it represents a new clinical entity is more difficult to ascertain Possibility of identity with measles seems unlikely because of its mild nature brief duration character of the skin eruption and absence of Koplik s spots Rubella is more difficult

(9) J A M A 155 544 548 June 5 1954

to exclude but absence of characteristic lymphadenopathy presumptive incubation period of about three to eight days and the season of maximal prevalence are not typical of rubella In roseola infantum degree and duration of pre eruptive fever are greater communicability is low and nearly all cases occur in children under 3 As described the skin eruption characteristic of erythema infectiosum or Fifth disease bears no resemblance The authors believe that the disease encountered in most of the patients although sharing some features of certain common exanthems probably is an infection sui generis Because the agents were isolated from feces rather than from blood other body fluids or tissues caution is necessary in drawing conclusions regarding their etiologic role Yet evidence suggests that these newly recognized agents are responsible for the disease

[Obviously tissue culture technics are going to enable us to distinguish and identify a number of these mild acute infectious diseases of childhood Herpangina pharyngoconjunctival fever and now this one which needs a name!—Ed]

Iceland Disease New Infection Simulating Anterior Poliomyelitis In late summer of 19 0 an epidemic occurred throughout New York State particularly the northern areas which spread into neighboring states to the south and east The diagnosis in most cases was acute anterior poliomyelitis abortive poliomyelitis or poliomyelitis suspect Distinctive manifestations were muscular aching dysesthesias and tenderness not only at onset but throughout the illness which lasted many weeks Symptoms of sensory tract and nerve involvement were frequent whereas muscle weakness and wasting were rare Believing that this was a new disease entity D Naldrett White and Robert B Burtch[1] made a thorough investigation of 17 cases with 2 more added later Confirmation of their opinion appeared in a report describing a clo ely similar outbreak in Iceland in 1948-49

Of the 19 patients 15 were women the sex ratio being regarded as probably artificial Average age was 30 When examined the disease had been present over two weeks in most Symptoms varied remarkably in intensity and type the most constant being pain and tenderness in the muscles particularly around the shoulders Symptoms suggestive of

(1) N I gy 4 06 516 J ly 1954

an upper or lower respiratory tract infection or gastrointestinal involvement appeared at the same time or soon afterward The third group of symptoms chiefly responsible for its confusion with poliomyelitis was neurologic In 13 patients there was transient weakness usually affecting the limbs and never accompanied by muscle wasting Deep reflexes were not involved Sensory symptoms were not infrequent 11 complained of paresthesias or numbness One patient lost joint position sense in the legs Another who complained only of numbness was found to have impaired joint position sense Two had sensory symptoms involving the ulnar distribution and one had symptoms over one sciatic nerve in all three nerve trunks were tender to pressure Another feature was marked mental depression observed in 11 patients Lymphadenopathy was present in four

Urine examinations showed no significant abnormalities White blood counts ranged from 4 900 to 10 000 with normal differential count Cerebrospinal fluid in all but two cases was normal as were chest roentgenograms Urinary creatine level was increased Serum examinations showed no immune bodies to poliomyelitis and no evidence of Coxsackie virus was found

Eight of the 19 patients were examined 15 months after the initial examination All had symptoms consisting of muscular aches and easy fatigue Four still had slight tenderness over the affected muscles only one had muscular weakness

The clinical symptomatology distinguishes these cases definitely from cases of acute anterior poliomyelitis The disease bears striking resemblances to that described by Sigurdsson and others in Iceland during 1948-49

[In the presence of an epidemic it could be recognized that this was a specific disease An isolated case especially in the later stages might easily be labeled as a functional or neurotic disorder —Ed]

ARTHRITIS

Comparison of Cortisone and Aspirin in Treatment of Early Cases of Rheumatoid Arthritis is reported by the Joint Committee of the Medical Research Council and

Nuffield Foundation on Clinical Trials of Cortisone ACTH and Other Therapeutic Measures in Chronic Rheumatic Diseases In a long term trial it was ethically out of the question to set up a control group on dummy treatment Therefore aspirin was selected for comparison with cortisone and the two drugs were allocated at random to two groups both receiving the same basic regimen of splints physiotherapy etc and being similar in regard to sex age duration of illness and treatment center Aspirin was disguised and cortisone was given in tablets or as a suspension in syrup Patients were asked not to take other drugs During the first year therapy was given in 12 week courses separated by one week off treatment Each course started with a standard dosage after which the physician was free to adjust the dose to suit individual requirements Specified courses for adults were given in divided doses not fewer than three times daily Doses of cortisone were 300 mg the first day 200 mg the second 100 mg the third to the seventh 50 mg daily during the second week and from the third to the twelfth week individualized at 25 200 mg daily with graded withdrawal in week 12 Dosage of aspirin was 6 Gm daily during the first week 2 Gm during the second week and individualized at 1 8 Gm thereafter with graded withdrawal in week 12 The cortisone group included 30 adults and the aspirin group 31

Side effects were recorded for 19 in the cortisone group and 21 in the aspirin group Most had more than one complication the most frequent in the cortisone group being moonface or rubicundity (11 patients) depression (5) and euphoria (4) and in the aspirin group tinnitus (11 patients) deafness (10) and nausea dyspepsia or anorexia (13)

Observations made 1 week 8 weeks 13 weeks and approximately 1 year after the start of treatment revealed that the two groups ran a closely parallel course in regard to joint tenderness range of movement in the wrist strength of grip tests of dexterity of hand and foot and clinical judgments of activity of the disease and of the patient s functional capacity Hemoglobin level and blood

(2) B r M J 1 1223 1 7 M y 29 1954

sedimentation rate were slightly more favorably influenced by cortisone

On each form of treatment the disease was judged at the end of one year to be inactive or only slightly active in about three fourths of the patients and some two fifths were regarded as capable of normal work and activity There appears to have been little to choose between cortisone and aspirin in management of these 61 patients in the early stages of rheumatoid arthritis Mean maintenance dose of cortisone being used at the end of the first year was 80 mg (25 125 mg) in 26 patients 4 were off treatment Mean maintenance dose of aspirin for 26 still on treatment was 4 5 Gm (1 13 Gm)

Management of Rheumatoid Arthritis with Prolonged Cortisone Administration W S C Copeman Oswald Savage Charles Dodds J H Glyn and M E Fearnley[3] treated 20 patients with rheumatoid arthritis at West London Hospital 14 received cortisone for more than two years and all continuously for at least a year All had had severe rheumatoid arthritis at least 2½ years (average 6 8 years) and none could carry out his normal occupation Rest salicylates and gold salt injections had failed to suppress progress of the disease

The dosage scheme originally suggested by Hench *et al* (300 200 and 100 mg on successive days) produced a too dramatic response which led to disappointment when this rate of progress did not continue Therefore routine initial dose was 100 mg daily with this it proved possible to measure the patient's response after about five days If response was adequate the initial dose was reduced by small amounts at intervals of not less than five days A maintenance dose of 50 mg a day or less was aimed at but could not always be achieved The dose occasionally had to be increased temporarily when conditions of extra stress occurred but was lowered again as soon as possible Average oral maintenance dose was 69 mg a day

Of the 20 patients who were initially unable to work 17 returned to their occupations and continued in them Functional improvement of patients receiving cortisone was greater than the actual degree of suppression of the

(3) B M J 1 1109 1113 May 15 1954

disease The most suitable cases are therefore those in which the functional disability exceeds the anatomic joint damage

Absolute contraindications to cortisone therapy are recent or active tuberculosis present or past psychosis or psychoneurosis diabetes *hypertension and severe osteo* porosis Long standing cases with much permanent irreversible deformity and joint damage are also contraindications Since cortisone is not actually curative and radiologic progression of joint damage has been seen in patients whose symptoms were suppressed the more conservative methods of treatment such as rest salicylates gold salts and physiotherapy should generally be tried first

The authors believe that cortisone therapy is a practical addition to treatment in selected cases of rheumatoid arthritis A number of patients previously incapacitated can be restored to relatively normal activity by long term treatment Such patients however require careful and constant supervision

Experiences of Prolonged Cortisone and ACTH Treatment in Rheumatoid Arthritis are reported by Nils Gewalli[4] Sixteen women and four men aged 27 64 were treated for more than a year with cortisone The initial intramuscular dose was usually 300 mg and they were maintained on oral doses of 50 75 mg Most patients had severe or moderately severe rheumatoid arthritis Before therapy some were bedridden with treatment they were out of bed moved about and performed their daily work Of the five severe ca es improvement in two was moderate and in three only slight More than half the moderately severe cases showed significant improvement When the preparation was withdrawn there was exacerbation of the disease process Oral administration was as effective as intramuscular injection in the same dose range

Side effects appeared in about 30% These were all mild however and in no case necessitated withdrawal of the hormone In many cases considerable improvement can be anticipated by use of cortisone and it is sometimes possible to render severely incapacitated patients fit to work part or full time

(4) A ta m d q 148 91 98 1954

Amyloidosis and Other Causes of Death in Rheumatoid Arthritis Per Olof Gedda[5] (Univ of Lund) reports data on 45 cases of active or inactive rheumatoid arthritis found among 10 914 autopsies Thirty six patients were females Age at death was 8-77 years most deaths occurring in the third to sixth decade The principal cause of death was infection—septicemia in eight pneumonia in five and tuberculosis in one Renal insufficiency was the second commonest cause in nine cases this was due to amyloid degeneration and in two to chronic diffuse glomerulonephritis In one of the latter secondary pyelonephritis was present In two other cases definite amyloid changes were found in the kidneys liver and spleen though amyloidosis was not the immediate cause of death Heart disease accounted for 10 deaths—myocardial infarction (2) valvular heart disease (2) hypertensive heart disease (1) and congestive heart failure or other nonspecified heart disease (5)

Average duration of arthritis in nine patients who died of uremia following amyloidosis was about 11 years Amyloid contracted kidneys were found in 7 of the 11 cases of amyloidosis Even though contracted kidneys do not develop subacute amyloid glomerulonephrosis may produce renal insufficiency with death from uremia in a comparatively short time blood pressure is not increased The four patients with amyloid nephrosis had normal or low blood pressures The adrenal cortex in two cases showed rich amyloid deposits with destruction of parenchyma in one of these peripheral circulatory insufficiency developed rapidly

The cause of amyloido is in rheumatoid arthritis is unknown In the autopsy material there were 86 cases of amyloidosis Tuberculosis was the basic disease in 41 The second highest incidence of amyloidosis was in rheumatic disease—11 of rheumatoid arthritis and 3 of rheumatic fever bronchiectasis was present in 7 ulcus cruris in 4 chronic pyelonephritis chronic pelviperitonitis and myeloma in 3 each hypernephroma in 2 and chronic osteomyelitis chronic perforating duodenal ulcer malignant lymphogranulomatosis and sarcoma of the skin in 1 each In five cases the cause of amyloidosis was unknown

(5) Acta med. sca di 150 443-45 1955

Signs of renal lesion in a patient with rheumatoid arthritis should arouse suspicion of amyloidosis When renal function is decreased and blood pressure remains normal or is low amyloidosis of the adrenals should be suspected

Diagnosis and Treatment of Reiter s Syndrome are discussed by Howard J Weinberger (Univ of California Los Angeles) and Walter Bauer[6] (Harvard Med School) The clinical triad of nongonococcic urethritis conjunctivitis and arthritis is commonly referred to as Reiter s syndrome after the case described by Hans Reiter in 1916 The condition usually occurs in men aged 20 50 rarely in male children and in men in the fifth decade The complete triad has not been reported in females Weight loss and fatigability and in about one third of patients a mild nonbloody diarrhea for one to three days may precede the acute on et Predisposing and precipitating factors are unusual

Urethritis or conjunctivitis may herald on et The *entire triad usually evolves in one to five weeks occasional*ly all three systems are involved simultaneously Most patients have fever (99 102 F) initially with temperature returning to normal in one to five weeks The initial attack may last 2 6 months although in some patients articular involvement may persist for 18 months Exacerbations involving any one system may occur during a single attack but prognosis for complete recovery in initial attacks is excellent Complete or partial recurrences occur months to years after onset in about 75% of patients but are usually less severe and of shorter duration than original attacks After repeated attacks a small number of patients may show chronic activity of the disease with persistently elevated sedimentation rates chronic articular involvement and progressive roentgen changes

Cutaneous lesions usually distributed over palms and soles conform clinically to keratosis blennorrhagica In severe cases the soles may be covered with heaped up crusts and fissured plaques Yellow waxy material may be heaped up under the distal end of the nail plate lifting of the nail from its base may result in its being shed Nails become opaque and brittle and the free border broken and

(6) M Cl N th Am 39 587 599 M h 1955

roughened The balanitis lesions in uncircumcised males appear as moist superficial 2-4 mm areas of ulceration on the corona extending to the urethral meatus

Mild conjunctivitis is usually the only ocular manifestation and may thus be overlooked Iritis and rarely keratitis may be seen Occasionally ocular involvement is severe and is the predominant feature It may last three months but recovery is generally complete without loss of vision

The articular involvement is almost always the most disabling and persistent feature Monoarticular arthritis has been observed but polyarticular involvement is usual the weight bearing and larger joints and spine being affected Suddenness of onset tendency to migration and degree of heat pain and tenderness suggest acute infectious arthritis

There may be stomatitis without obvious cutaneous lesions Diarrhea is seen often enough to suggest that it is an important part of the syndrome Rarely acute myocarditis is found There are mild to moderate leukocytosis elevation of sedimentation rate lowering of the hematocrit and pyuria Prostatic and urethral secretions show abundant pus cells and grossly bloody urine with abacterial cystitis may be a manifestation Pleuropneumonia like organisms have been recovered from synovial fluid in two patients and from the genitourinary tract in a high percentage but their significance in relation to Reiter s syndrome cannot be evaluated until more is known of their origin and nature

Three cardinal points in diagnosis are (1) abrupt onset of the triad (2) repeatedly negative smears and cultures for gonorrhea and other pathogenic organisms (3) the usually self limited course In differential diagnosis gonorrhea arthritis complicating bacillary dysentery erythema multiforme bullosum and rheumatoid arthritis with psoriasis of a pustular type must be considered

Because of the self limited course evaluation of therapy is difficult Sulfonamides fever therapy foreign protein inoculations arsenicals gold salts and penicillin have had no definite influence on the course Streptomycin 1 Gm daily or tetracycline 250 mg four times a day may lessen the severity of genitourinary involvement Corticotropin or cortisone may lessen articular pain swelling inflammation and fever however these symptoms usually return promptly when the drug is stopped For symptomatic re

lief aspirin splinting of affected joints and hot packs two or three times daily are effective Bed rest is indicated until fever and involvement of weight bearing joints have subsided with restricted activity as long as acute or subacute articular inflammation is present

HELMINTHIASIS

Fulminating Trichinosis with Myocarditis Louis D Fey and Moore A Mills[7] (Seattle) report a case

Man 47 with fever malaise and generalized aches four days before had noted dizziness weakness on exertion frontal headache thigh pain urinary frequency and burning and swelling of the eyes

On physical examination the only pertinent findings were temperature of 102 8 F pulse 120 blood pressure 110/70 injected and swollen conjunctivas and granular and edematous pharynx Laboratory studies showed nothing remarkable Two days later he appeared gravely ill Oral temperature was 103 pulse 150 blood pressure 100/50 Periorbital edema was pronounced and cardiac enlargement and a blowing systolic murmur were noted Roentgenograms of the chest revealed cardiac enlargement and interstitial edema of the middle and both lower lobes ECG revealed a left bundle branch block He was hospitalized and his course was marked by septic temperature fluctuating between 101 and 104 F gradually subsiding by lysis He remained toxic and somewhat disorientated during the first four days after admission The murmur noted previously soon disappeared Leukocytes numbered 11 960 and 16 eosinophils were noted on smear Because of rising eosinophil count normal sedimentation rate interstitial edema hypertension and myocarditis trichinella infestation was suspected and muscle biopsy was performed This revealed two worms in the pre encystment stage surrounded by giant cell foreign body reaction On questioning it was found that he had eaten large quantities of raw mettwurst sausage over a period of days Seventeen other cases of trichinosis were subsequently traced to the market from which he purchased this product

After discharge he continued to have fever at night associated with drenching p rspiration During the ensuing months he experienced frequent episodes of dyspnea orthopnea fatigue weakness and fainting spells He died three years after onset in acute congestive heart failure Autopsy revealed a greatly enlarged heart with some sclerosis and narrowing of the coronary vessels Microscopic sections showed focal type myocarditis Larvae were not seen in the myocardium but were readily found in skeletal muscle Death was ascribed to myocarditis and cardiac failure secondary to infestation with Trichinella spiralis

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(7) N rthw t M d 53 701 706 J ly 1954

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(7 t Med 53 701 06 J ly 1954

before death in congestive failure but the case for attributing this to myocarditis of trichinal etiology does not appear to be firmly established Myocarditis may be a feature of the acute stage of trichinal infestation but in most if not all cases the process subsides completely if the patient survives the acute phase —Ed]

Trichinosis Report of Case Manifesting Myocarditis Encephalitis and Radial Neuritis Response to ACTH Review of Literature Regarding Erythrocyte Sedimentation Rate is presented by Dan C Roehm[8] (Vanderbilt Univ) Man 34 was hospitalized in amnesia Three weeks before he had had nausea vomiting and watery diarrhea several days before severe weakness and amnesia were noted Shortly after admission his condition suddenly deteriorated Temperature rose to 103 F and pulse to 140 blood pressure fell to 80/60 He was unable to move any extremity and was incontinent and disoriented Wristdrop soon developed Following intravenous infusion of 20 mg corticotropin and 40 mEq /L KCl all evidence of acute toxicity disappeared Considerable clinical improvement followed repeated administration of corticotropin Muscle biopsy revealed Trichinella spiralis Electrocardiograms taken at intervals during the illness were diagnostic of myocarditis the most serious complication of acute trichinosis Sedimentation rate remained normal throughout the acute febrile phase

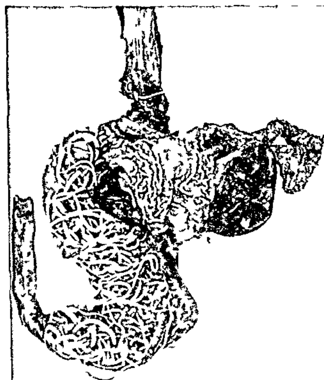
A review of the literature with respect to erythrocyte sedimentation rate (ESR) indicates that normal values are common particularly in the acute uncomplicated disease The relatively low ESR probably is an integral part of the hematologic response in acute trichinosis and is a manifestation of the serum sickness like nature of the illness When the hypersensitive stage has passed delayed elevation may occur In four published reports of fatalities when eosinophils had disappeared from the peripheral blood the ESR remained as the only hematologic indication of the allergic nature of the underlying disease A relatively low ESR in a clinical syndrome suggesting inflammation and tissue destruction may lead to proper consideration of acute trichinosis

[The author s evidence of normal sedimentation rate in acute trichinosis looks like a pearl —Ed]

Pathologic Aspects of Ascariasis are described with six illustrative cases by McKenzie P Moore Jr[9] (Med College of South Carolina) The adult worms of Ascaris lumbricoides normally inhabit the small intestine and sub

(8) A I t M d 40 1026 1040 M y 1954
(9) So th M J 47 825 832 S pt mb 1954

sist on chyme Fully embryonated ova containing second stage larvae are ingested by the human host In the small intestine having penetrated the wall and entered the lymphatics and venules the larvae go to the right heart and lungs either directly by the lymphatics or indirectly



Fg 14—Ad lt d t m h d t tın (Co t y f M M P Jr S th M J 47 8 5 83 S pt mb 1954)

through the portal vein and liver In the lungs after penetrating the capillaries to enter the alveolar spaces they moult twice within 10 days and ascend the bronchi and trachea to be swallowed again In the intestine they undergo a fourth moult approximately four weeks after infection grow into adult worms mate and in another six weeks the females deposit ova

before death in congestive failure but the case for attributing this to myocarditis of trichinal etiology does not appear to be firmly established Myocarditis may be a feature of the acute stage of trichinal infestation but in most if not all cases the process subsides completely if the patient survives the acute phase —Ed]

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(8) Ann Int Med 40 10 6 1040 M y 1954
(9) S uth M J 47 8 5 832 S pt mb r 1954

Role of Streptococcus in Pathogenesis of Rheumatic Fever is discussed by Frank J Catanzaro Chandler A Stetson Alton J Morris Robert Chamovitz Charles H Rammelkamp Jr Bertrand L Stolzer and William D Perry[1] (Cleveland) Despite evidence that group A streptococci are responsible for rheumatic fever these organisms have been isolated from only 50-60% of patients during acute phases of the disease The authors have demonstrated that they can be isolated from all patients six weeks after a streptococcic illness if special bacteriologic procedures are used It appears likely therefore that most rheumatic subjects harbor the organism at the onset of an acute attack

Penicillin therapy markedly reduces the attack rate of rheumatic fever decreases the antibody response and eradicates the streptococcus from most patients Since rheumatic patients frequently exhibit an exaggerated response to streptococcic antigens inhibition of antibody production must in some way be responsible for prevention of rheumatic fever On the other hand despite a low antibody response following an infection treated with various antibiotics rheumatic fever still developed in a few patients Analysis revealed that most of them continued to harbor the infecting type of streptococcus Thus it appeared that persistence of the streptococcus after infection might be significant in the pathogenesis of rheumatic fever

To determine the relative importance of group A streptococcus and of excessive antibody production patients with streptococcic infections were treated by one of three methods Treatment with penicillin nine days after onset of illness eliminated the infecting organism from the throat failed to inhibit antibody formation appreciably and significantly reduced the attack rate of rheumatic fever Administration of sulfadiazine during the acute streptococcic illness suppressed antibody formation somewhat more effectively than penicillin at 21 days but did not eradicate the organism nor prevent rheumatic fever Patients who received no specific therapy sustained maximal antibody

(1) Am J M d 17 749 756 Dec mbe 1954

Usually passage of ascaris larvae through the alveolar walls of the lungs causes only mild respiratory infection but sometimes symptoms of pneumonitis (ascaris pneumonia) occur when many larvae are present in the alveolar spaces simultaneously

In the intestine complications of ascaris infestation vary from mild colicky pain due to mechanical or toxic mucosal irritation to obstruction volvulus or intussusception caused by balls of entwined worms That the adult worms migrate and often crawl into small openings such as the vermiform appendix is well known Any portion of the gastrointestinal tract may be perforated by migration Migration into the ampulla of Vater common bile duct or pancreatic duct causes abscesses

Negro girl 4 was dead on arrival at hospital One of 10 children whom the mother routinely wormed every three months she became ill 36 hours before when with all the children she received a dose of a proprietary antihelminthic before breakfast While eating she had abdominal pain and suddenly vomited two round worms. She played and appeared well the rest of the day despite two more vomiting episodes producing worms She slept well but was very ill and weak the next morning complaining of intermittent abdominal pain On examination at the hospital round worms were found in the nose and mouth Clinical diagnosis was helminthiasis

At autopsy one round worm was found in the left pleural cavity and five in the right Both cavities communicated with the esophagus by three longitudinal perforations 1 cm long situated above the esophageal hiatus The peritoneal cavity contained 125 cc serosanguineous fluid and the retroperitoneal area was conspicuously hemorrhagic The gastrointestinal canal contained 330 A lumbricoides varying in size and length up to 30 cm long Most were in the stomach duodenum and first portion of the jejunum almost obstructing the lumen (Fig 14) In the region of the pancreatic neck a sharp line demarcated normal and abnormal tissue The entire body and tail of the pancreas were firm and bluish black with pronounced hemorrhagic discoloration of surface and surrounding tissue Two round worms in the pancreatic duct caused complete obstruction where the hemorrhagic discoloration began a third occupied a necrotic cystic space in the pancreatic tail No worms were found in the biliary system Histologically the wall of the pancreatic duct was thin with the entire mucosal surface atrophic or sloughing and with ulceration in some areas The parenchyma showed every stage from normal to complete coagulation necrosis Perforations of the esophagus were apparently a postmortem change since no histologic evidence of inflammatory reaction was seen

influenced by hormone therapy in some patients Findings in regard to the rash erythema marginatum with respect to cortisone therapy are inconclusive

Results in collected cases support the probability that cortisone and ACTH in adequate doses do benefit acute rheumatic pericarditis When tachycardia occurs with high fever in the acute phase a dramatic slowing may be expected to follow administration of the hormones Tachycardia not associated with high fever shows far less striking or uniform response The author cites five cases of carditis with congestive failure in which failure cleared rapidly during hormone therapy without digitalis or diuretics in three more additional measures were required Effect of cortisone and corticotropin on cardiac enlargement is difficult to evaluate because of the role pericardial effusions may play Their effect in preventing cardiac valvular damage as shown by changes in murmurs is also difficult to assess because of subjective factors especially in interpreting systolic murmurs It is certain however that established murmurs resulting from damage incurred in previous attacks are not affected by hormones

Serious side effects from hormone therapy occurred infrequently in the author s cases One girl 16 became mildly psychotic but recovered with electric shock therapy In three children hormones had to be stopped because of hypertension with diastolic pressures above 100 mm In some patients pigmentation in its early stages suggested cyanosis Liver enlargement also can be misinterpreted as due to heart failure unless it is recognized that fatty infiltration can occur Both these last effects subside when the hormone is stopped

Paradoxically co operative study of the value of cortisone corticotropin and salicylates in rheumatic fever has again raised the question whether salicylates may not exert a beneficial effect on heart lesions The dogma that salicylates do not benefit carditis has been so firmly fixed that it has been surprising to find that in a carefully conducted analysis of many patients those who received salicylates fared about as well as those treated with cortisone and ACTH At the same time evidence that these hormones are beneficial when given early in carditis has led

formation remained carriers and experienced the usual attack rate of rheumatic fever

The data indicate that it is probably advisable to administer penicillin in the early phases of acute rheumatic fever under the assumption that eradication of the streptococcus may influence the rheumatic process Even though a drug favorably influences the acute symptoms it should not be used in streptococcic infections unless adequate bacteriologic studies establish that it results in elimination of streptococci from the respiratory tract For this reason sulfadiazine or other sulfonamides should never be used in treatment of streptococcic infections

Eradication of streptococci by penicillin was followed by a prompt fall in new cases of rheumatic fever an indication that living streptococci must be present in the oropharynx or elsewhere for rheumatic fever to develop This conclusion conflicts with hypotheses previously advanced to explain the pathogenesis of rheumatic fever but may be in accord with the concept that hypersensitivity of the tuberculin or delayed type is involved

[The implication from these studies is that there must be living streptococci in the host's tissues in order for rheumatic fever to develop If this be true it is probably good practice as recommended by McEwen (following article) to give penicillin in treatment of acute rheumatic fever —Ed]

Treatment of Rheumatic Fever with particular reference to penicillin cortisone and ACTH and the possible beneficial effect of salicylates on carditis is discussed by Currier McEwen (New York Univ) Although knowledge of the over all value of cortisone and ACTH in rheumatic fever is incomplete it is helpful to consider their effects on individual manifestations of the disease There is no doubt about their beneficial effects on polyarthritis fever and general toxic state Doses of 25 mg cortisone by mouth four to six times daily cause dramatic relief of these symptoms within 12-48 hours but full doses of salicylates (0 06 Gm /lb) accomplish essentially the same results More recent studies comparing cortisone or corticotropin and salicylate show little or no difference in effect on subcutaneous nodules a fact which has an indirect bearing on the value of hormone therapy in carditis Chorea may be

(2) Am J Med 17 794 803 December 1954

preclude the necessity of prolonged use The relative freedom from side effects was attributed to the short period of treatment and the absence of congestive failure and liver dysfunction in all patients but one This patient who was in congestive failure on admission became worse with each of three courses of therapy and had multiple side effects

During therapy fluoroscopy showed unusual and characteristic changes in the heart i e marked dilatation of both ventricles a meal sack drooping of the heart onto the diaphragmatic surface as though the muscle tone were decreased and a slow weak undulating accordion like contraction These changes appeared within 24-48 hours after the first injection of corticotropin and disappeared rapidly within 48 hours after cessation of the drug They may be due to edema of the heart muscle associated with retention of water and sodium caused by corticotropin

[This study suffers from lack of a control series a drawback guarded against in the elaborate co-operative study carried out in Britain and the United States (see next article) Nevertheless the results described here employing comparatively large doses of ACTH are impressive and one would like to see this plan tried more extensively —Ed]

Treatment of Acute Rheumatic Fever in Children Co-operative Clinical Trial of ACTH Cortisone and Aspirin is reported by the Rheumatic Fever Working Party of the Medical Research Council of Great Britain and the Sub committee of Principal Investigators Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association[4] Six centers in the United Kingdom five in the United States and one in Canada collaborated in an attempt to assess the relative effectiveness of each of the hormones and of aspirin in altering the course of acute rheumatic fever or in suppressing its clinical manifestations and in preventing rheumatic heart disease All patients were hospitalized and on bed rest and were protected against beta hemolytic streptococcic infection

Precise diagnostic criteria were necessary to insure that all patients had unquestionable rheumatic fever Five major and five minor manifestations were defined The former included carditis polyarthritis chorea subcutaneous nodules and erythema marginatum the latter fever elevated

(4) Brit M J 1 555 574 M 5 1955

to obvious conjecture that perhaps salicylates too may be of help

A suggested plan of treatment of rheumatic fever follows (1) Sufficient penicillin should be given at once to eradicate the hemolytic streptococcic carrier state (2) Prophylaxis should then be begun and continued indefinitely to prevent further infection with hemolytic streptococci (3) If there is no evidence of carditis salicylate alone probably is preferable to hormone therapy (4) In the presence of carditis cortisone should be started at once in doses of 300 mg daily by mouth and continued six weeks after which dose is reduced half a tablet (12 5 mg) daily Because of the salt retaining effect of cortisone a rigid diet containing less than 50 mg sodium daily is imperative Potassium chloride is given in doses of 1 Gm two or three times daily

Corticotropin in Rheumatic Carditis Beneficial Effects of High Dosage and Short Duration in Acute Exacerbation of Chronic Rheumatic Carditis Although since 1949 cortisone and corticotropin have been widely used in rheumatic fever to control the exudative phase there has been little uniformity in dosage or in length of therapy nor has the effect on the proliferative phase been shown In this study Nathan M Greenstein[3] (New York) used corticotropin in high doses for short periods to determine if the proliferative phase could be controlled and if the period of rheumatic activity could be shortened without undue side effects Twenty girls and eight boys aged 6 11 with acute rheumatic fever and definite carditis were treated with 75 mg corticotropin intramuscularly every 6 hours for 14 18 days Potassium salts were not given since previous studies had shown they were rarely necessary All children received 300 000 units of penicillin daily

The drug was stopped abruptly in all cases but no rebound effects were noted except a sharp rise in eosinophil count There was no rise in pulse rate temperature or erythrocyte sedimentation rate and no electrocardiographic change It was thus concluded that the exudative phase was controlled and the period of activity actually shortened and not just suppressed This indicates that large doses

(3) A M A Am J Dis Child 87 694 704 J 1954

was balanced by a greater tendency for the acute manifestations to reappear for a period on cessation of treatment Hormone treatment also led to more rapid disappearance of nodules and soft apical systolic murmurs However at the end of one year the proportion of patients with residual cardiac damage was similar in the three groups There was no evidence that any of the three agents resulted in uniform termination of rheumatic fever in children and on all treatments some patients developed fresh manifestations during therapy

[All enthusiastic reports on benefit from steroid therapy will have to be evaluated in the light of this carefully planned large scale clinical trial One possibility to be considered in evaluating these results is that aspirin has some beneficial effect consequently the end results in all three groups may have been somewhat better than would have been the case without any treatment —Ed]

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic Lupus Erythematosus Review of Literature **and Clinical Analysis of 138 Cases** are presented by A McGehee Harvey Lawrence E Shulman Philip A Tumulty C Lockard Conley and Edyth H Schoenrich[5] (Johns Hopkins Univ) Initial manifestations may be so vague that onset cannot be ascertained The patient may always have been sensitive to sun, had recurrent mild aching joints since childhood or fail to report some apparently unrelated past incident e g pleurisy or a skin eruption The observer may be uncertain whether a past pneumonia or outbreak of hives was due to systemic lupus erythematosus (SLE) Clinical diagnosis can be made consistently only if it is appreciated that the disease often unfolds episodically over many years In case of a disorder of a single organ system such as arthritis search must be made for possibly significant past illnesses

Average age of the 138 patients at onset was 29 78% were females Of 105 patients all but 10 had joint involvement often early and in 63% during the initial episode Hands wrists elbows shoulders knees and ankles were most commonly implicated Severity of discomfort and objective evidences of arthritis were usually disproportionate

(5) M d 33 291-437 D mb 1954

sedimentation rate evidence of previous streptococcic infection increased P R interval and reliable history of rheumatic fever For inclusion in the study the patient must have had (1) at some time during the illness two major or one major and two minor manifestations and (2) on the first day of therapy one major manifestation or two of the following—fever elevated sedimentation rate increased P R interval

Patients were divided into two age groups 0 15 years and 16 and over and into three duration from onset groups 14 days or less 15-42 days and 43 days and over Allocation to treatment plan was both blind and random Each center received serially numbered and sealed envelopes containing statements of treatment The investigator at the treatment center had only to open the next available envelope for the particular age and duration from onset group to ascertain the treatment to be applied

Dosage schedule for ACTH was 80 USP units daily for four days 60 units for the next three days 40 units the second and third weeks 30 units the fourth and fifth weeks and 20 units the sixth ACTH dosage in U S patients was increased after a lack of dramatic response in the first few patients in an attempt to achieve optimal dosage Cortisone was given in total daily dosage of 300 mg the first day 200 mg the next four days 100 mg for the rest of the first three weeks 75 mg the fourth and fifth weeks and 50 mg the sixth week Aspirin dose calculated on basis of body weight was 60 mg /1 lb daily or 10 Gm whichever was less the first two days 40 mg /lb (or 10 Gm) the next five days 30 mg /lb for the next five weeks Aspirin was given orally every 4 hours for 48 hours every 6 hours thereafter All patients were observed for three weeks after completion of therapy

Data for 497 patients under age 16 were analyzed A large proportion of patients were found to be in early stages of the disease and had no established heart disease There were six deaths one in the ACTH two in the cortisone and three in the aspirin group Results of treatment were measured in relation to the separate manifestations of the disease With ACTH or cortisone there was more prompt control of certain acute manifestations but this

one episode of pleurisy (usually dry) and 14 repeated attacks

Typical vascular lesions in the gastrointestinal tract have been reported Manifestations have included anorexia nausea vomiting diarrhea and severe abdominal pain Generalized lymphadenopathy was present in 37%

Some nervous system abnormality developed in 37% of patients 18 had convulsions (5 with hemiplegia 1 with motor aphasia and 4 with toxic psychosis) and 20 had one or more acute psychotic episodes Neurologic dysfunction almost invariably developed during an active phase of the disease

Retinal lesions consisting of fluffy exudates due to ganglifrom degeneration of nerve fibers (so called cytoid bodies) are helpful in differential diagnosis of SLE when present with other suggestive signs They may be transient and repeated funduscopic examinations should be done

Hematologic abnormalities occur in virtually all cases The L E cell is the only specific change but other alterations are fairly characteristic The high incidence of anemia has often been emphasized Anemia usually results from retarded erythropoiesis but occasionally a hemolytic process may be important Leukopenia (white cell count below 6 000) has been reported in 25 85% of cases It tends to be associated with an increase in neutrophils Extreme leukopenia (below 2 000) is unusual Leukocytosis (counts up to 30 000) has been described with complicating infections or occasionally during exacerbations Purpura is common In 23 of 86 patients platelet counts were at times abnormal Twelve had severe thrombocytopenia with counts less than 50 000 Occasionally thrombocytopenic purpura is the outstanding feature and may occur when other signs are trivial or may antedate them by months or years Idiopathic thrombocytopenic purpura has been diagnosed The platelet count may become normal spontaneously or after splenectomy A history of joint pain pleurisy skin eruption or other manifestation may be significant in a patient with thrombocytopenic purpura Two patients had a hemorrhagic disorder associated with a coagulation defect caused by a peculiar circulating anticoagulant probably an abnormal

Skeletal deformities often accompanied chronic involvement Arthritis was rheumatoid in 28 cases Some patients had marked contractures muscle atrophy and joint deformity others had severe pain for years without disability or deformity

All but 16 of 105 patients had some cutaneous manifestation in 31 as the initial sign Areas most often involved were face neck V area of chest arms fingers and legs Erythematous scaling pruritic lesions sometimes patchy sometimes coalescing to involve a wide area were the most common There was often marked vascularization with small telangiectasias An erythematous blush frequently violaceous was common on the malar eminences (butterfly appearance) Raynaud s phenomenon (10 patients) preceded other manifestations by many years always associated with arthritis Ten patients had tender subcutaneous nodules near large joints Purpuric lesions were common *and were associated with thrombocytopenia in 16* Mucosal lesions usually oral and appearing during an acute episode accompanied skin changes in 15 In three patients chronic discoid lupus suddenly changed to acute systemic involvement

Chronic nephritis is common and the *wire loop lesion* in glomerular capillaries found at about 60% of autopsies is thought to be pathognomonic This lesion consists of an irregularly thickened basement membrane which stains intensely with eosin and involves one or several capillary loops *Mild renal disease* without significant renal insufficiency was present in 41 patients and moderate to severe renal disease in 24 12 patients died of uremia

The pericardium myocardium or endocardium was involved in 55% of patients Pericarditis was present in 48% as the initial *sign in a few In a third of the patients on* whom autopsy was done verrucous bacterial vegetations (Libman Sachs) were found

Intrinsic pulmonary involvement was present in 46 patients In 20 changes were considered due to SLE 6 had tuberculosis 5 lobar pneumonia 2 lung abscesses 9 lobular pneumonia 2 aspiration pneumonia and 1 repeated hemoptyses Pneumonitis due to lupus is often hard to differentiate from bacterial infection Sixty patients had

by essentially complete remission for several months When relapse followed a long remission another course of treatment was given If no lasting remission followed a single course continuous maintenance therapy was given Remissions following rebound lasted 1-47 months There appear to be no significant differences between ACTH and cortisone in remission pattern or development of rebound On Aug 1 1953 18 of the 62 patients were dead and the status of 2 was unknown Of the 42 living 25 were not on treatment 19 were asymptomatic or had mild activity after one or more courses of ACTH or cortisone and 6 were seriously ill Seventeen were on hormone treatment There was no correlation between persistence of L E cells and completeness of clinical remission

[This important clinical analysis will undoubtedly be considered one of the classic papers on systemic lupus erythematosus for many years to come It is an exceedingly valuable reference containing information on many of the questions which arise in clinical discussions —Ed.]

Nitrogen Mustard in Treatment of Systemic Lupus Erythematosus Edmund L Dubois[6] (Univ of Southern California) reports results with 34 courses of nitrogen mustard intravenously and 11 courses of triethylene melamine (TEM) orally in 20 patients with acute and subacute systemic lupus erythematosus Mustargen® was usually given in the evening in a single dose of 20 mg injected into the tubing of an intravenous infusion of 5% dextrose in water approximately 0 4 mg /kg after premedication with 0 1 Gm phenobarbital and 0 1 Gm pentobarbital sodium Triethylene melamine in 5 mg tablets was taken with water on an empty stomach one hour before breakfast Initial courses consisted of a total dose of 10 15 mg Hemoglobin and white blood cell counts were normal before each dose The interval between courses was not less than two weeks Despite cortisone or corticotropin maintenance therapy all patients were going down hill

Best results were obtained in edematous patients with nephrotic nephropathy the greater the edema the more spectacular the result Most of these patients did not respond to mercurials with ammonium chloride In 3 14 days after nitrogen mustard was given diuresis began in three

(6) A.M A A h I t. M d 93 667 67 M y 1954

globulin Clotting time was considerably prolonged in four others In seven prothrombin time was moderately and in six markedly prolonged

L E cell tests performed in 96 cases, were positive in 79 the cells could not be demonstrated in 17 cases of un equivocal SLE Although isolated cases have been report ed in which L E cells were found supposedly without other evidence of SLE in many hundreds of tests it was found that every patient with L E cells had a clinical dis order compatible with the diagnosis of SLE In over 700 cases of a great variety of diseases L E cell tests were negative

Positive erologic reactions for syphilis in SLE are mostly biologic false positive reactions of chronic type i e there is no identifiable precedent acute infection and reagin persists indefinitely probably for life Standard syphilis tests were positive at least once in 38 of the 138 cases Treponema immobilization tests done in 20 were positive in 7 The patients had both SLE and syphilis

The clinical course may extend over many years or may be fulminant lasting only a few months or weeks A protracted course with exacerbations and remissions dur ing which various organ systems are implicated is charac teristic Spontaneous remissions developed in 34 patients who had not received hormone therapy Usual remission was 1-4 years but occasionally 10 years or longer Twelve patients had more than one remission

Pregnancy occurred once in six and twice in five pa tients without definite effect in several In four SLE first occurred during gestation One patient had a complete re mission with disappearance of L E cells during two preg nancies but symptoms recurred within four weeks after delivery

Of 62 patients treated with ACTH or cortisone most had a satisfactory immediate response but in some sympto matic control was difficult even with intensive treatment and some required continued treatment over long periods After hormone withdrawal treatment was not reinstituted for at least a week unless the patient became extremely ill In some instances relapse the first week after therapy was temporary (rebound phenomenon) and was followed

by essentially complete remission for several months When relapse followed a long remission another course of treatment was given If no lasting remission followed a single course continuous maintenance therapy was given Remissions following rebound lasted 1-47 months There appear to be no significant differences between ACTH and cortisone in remission pattern or development of rebound On Aug 1 1953 18 of the 62 patients were dead and the status of 2 was unknown Of the 42 living 25 were not on treatment 19 were asymptomatic or had mild activity after one or more courses of ACTH or cortisone and 6 were seriously ill Seventeen were on hormone treatment There was no correlation between persistence of L E cells and completeness of clinical remission

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(6) A M A A h I t M d 93 667 672 M y 1954

of five patients In a few weeks serum proteins returned to normal and urinary sediment improved Dosage of cortisone was not altered for several weeks before nitrogen mustard therapy or during the period of improvement In seven patients without overt renal damage there was no effect on their skin lesions joint pains maintenance dose of cortisone or hypertension In no patient in this series was full remission induced by nitrogen mustard so that cortisone therapy could be stopped In an addendum Dubois reports on four more patients with the edematous type of nephropathy treated successfully with nitrogen mustard intravenously

Reactions to intravenous therapy were nausea and vomiting in about 80% and occasionally localized phlebitis Transitory leukopenia lasting about a week appeared 7 10 days after therapy Antibiotics were not given

Two of five patients given TEM by mouth had nausea One had transitory leukopenia two had none In one patient three weeks after a second dose of 10 mg (total 25 mg) white cell count fell to 300 and platelets disappeared after vigorous antibiotic and cortisone therapy she recovered The fifth patient received 15 mg and two weeks later 10 mg with no change in the hemogram Five weeks later with a normal white cell count she received 15 mg more and two weeks afterward the leukocyte level was 3 100 She died of aplastic anemia six weeks after the last dose despite massive doses of antibiotics and cortisone Possibly lupus patients are more sensitive to TEM but because of its erratic toxicity Dubois has ceased using it

Lupus Erythematosus Like Syndrome Complicating Hydralazine (Apresoline®) Therapy progresses from mild arthralgia to a clinical picture of rheumatoid arthritis and finally simulates disseminated lupus erythematosus with appearance of L E cells in the peripheral blood David J Reinhardt and Jerome M Waldron[7] (Pennsylvania Hosp Philadelphia) report a case with histologic findings

Negress 48 with moderately severe essential hypertension received hydralazine 400 mg daily with cation exchange resins for five months and then other hypotensive drugs for two months Combined therapy of 600 mg hydralazine with dibenzyline® and protoveratrine was given for six months after which blood pressure

(7) J A M A 155 1491 1492 Aug 21 1954

rose and pain and edema of the hand appeared This wa ... ll w d by generalized migratory swelling and pain in the joints which h appeared promptly after antihypertensive medication wa t ... l In investigating the cause of these manifestations the ... r given individually Twelve days after reinstatement of hydrala in marked edema of the right hand appeared followed by acut ... tory arthritis with fever of 99 to 102 6 F Both knee ankl ... and wrist and all fingers were swollen and tender ... (s ars with keloid and atrophy) showed enlargement with ... dep gr entation Red blood cell count hemoglobin level ... tocrit value were unchanged Urine showed a trace ... Se um globulin was 4 1 Gm One of three tests for ... peripheral blood gave a positive reaction Biop ... reveal d marked collagenous scarring containing ... lagenous necrosis with fragmentation and nuclear debri ... fibrocy ic respon e A rheumatic nodule showed ... collagen necrosis surrounded by fibroblasts and mononu ... with rare binucleated and trinucleated giant cells Compl ... obtained with cortisone but attempts to reduce th ... weeks two months and three month later resulted ... febrile arthritic episode

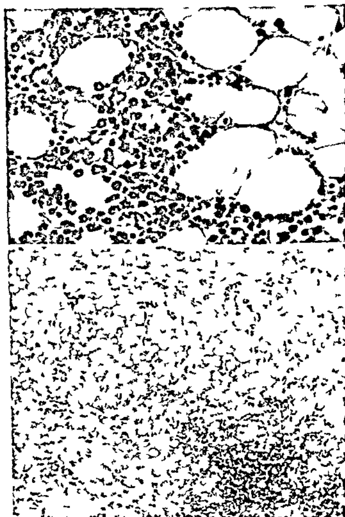
Presence of a typical subcutaneous rheumati ... acute collagenous necrosis in the skin biopsy ... of rheumatoid arthritis and lupus erythemat ... ing that hydralazine actually can produce the di ... This case underlines the danger of continuing hydralazine ther apy reproduction of symptoms produced an ... that persi ted de pite withdrawal of the drug

[Qui e a few cases of this lupus like syndrome have ... ti nts treated with hydralazine (apresoline®) Usually ... drome subsides spontan ously on withdrawal of the drug ... tells us in connection with the pathogenesis of true systemi ... mato us cannot yet be defined —Ed]

CHRONIC INFLAMMATORY SYNDRO... OF UNCERTAIN ETIOLOGY

Weber Christian Disease Survey with Report o Ca e is presented by Bodil Nexmand Hauge and Tor Chri ... sen[8] (Oslo) This disease is characterized by recu... attacks of subcutaneous nodulation *with fever* The ... nodules 1 10 cm in diameter located on the trunk ... extremities particularly the thighs are usually tender with bluish red discoloration of overlying skin when sit

(8) A t m d a d 150 193 198 1954



F g 15 (t p) – Subcutaneo s nod l w th ch r t t c p n cul t H ma to yl eo n ×400 (pp x)
F g 16 (bottom) —L ve show g necr s s nd fatty d gener t on H mat yl n o n 80 (pp)
(Co rte y f H uge B N d Ch l t ans n T Acta m d s nd 150 193 198 1954)

uated superficially Initially the infiltrates are freely movable During involution the overlying skin becomes pigmented and often atrophic with slight depression of the central area Pyrexia persists as long as the infiltrates are present Age distribution of reported cases is 2-64 years most patients being relatively young women So far as is known only four deaths have been reported except for five patients who died of intercurrent disease

Woman 44 had increasing fever and subsequent subcutaneous infiltrates involving the trunk and extremities that were covered by brownish or bluish red skin and were ulcerated in some areas During hospitalization fever was continuous sometimes spiking While new infiltrates increased some old ones disappeared leaving depressed scars Hemogram revealed moderate anemia leukopenia and relative lymphocytosis and biopsy of a skin nodule showed panniculitis (Fig 15) Antibiotics a etylsalicylic acid ACTH and cortisone were ineffectual Her condition deteriorated steadily Severe leukopenia and thrombocytopenia developed and she died about seven months after onset At autopsy the liver was enlarged and exhibited fatty degeneration hemorrhage and necrosis (Fig 16) A cutaneous nodule showed the same picture as on previous biopsy Other organs were normal

In all cases in which autopsy has been performed nonspecific fatty infiltration and necrosis of the liver were found Necrosis of the peripancreatic fat tissue has also been described Relation between fatty necrosis of the liver and panniculitis is obscure In the present case fatty infiltration and necrosis were seen only in the liver

Connective Tissue Manifestations of Neoplastic Disease of various types are reviewed by John Lansbury[9] (Temple Univ) Relation between malignancy and the dyscollagenoses is not coincidental since connective tissue reactions may disappear following resection or irradiation of the cancer The connective tissue reaction may take the form of the Bamberger Marie syndrome especially in bronchogenic carcinoma or of a variety of dyscollagenoses most common of which are arthritis and dermatomyositis Connective tissue manifestations usually precede localizing signs of the malignancy itself

The shifting arthralgias in children and adolescents may especially in subleukemic states cause difficulty in diagnosis as they may mimic rheumatic fever

(9) G t e 9 319 3 4 J ly 1954



F g 1 (p) —b b u d i w th l t t 1 l H m t Fa 16 (b tt)—L h w g ec d f tty d g n n H m t xyl n 80 (pp) (Cou t sy f H g B N d Ch t n T A t m d d 150 193 198 1954)

toms may be strikingly relieved within 24 hours after removal of a bronchogenic carcinoma —Ed]

Case of Primary Granulomatous Phlebitis M O Donnell and J D Kennedy[1] (Galway) report a case of prolonged pyrexia associated with thrombophlebitis of the superficial veins

Man 31 had fever associated with pains in knees and ankles for about 10 days and pain in the interphalangeal joints of the right little finger for 1 day Provisional diagnosis was subacute rheumatic fever and salicylate was prescribed Pyrexia continued and vomiting and abdominal pain caused considerable weight loss No splenic enlargement was detected Leg pains were intermittent After two weeks pain and patchy tenderness developed on the flexor surfaces of the forearms on the left superficial veins were hard and tender red lines being evident on the overlying skin Slight albuminuria was found a month later lasting two weeks Biopsy showed an unusual granulomatous condition involving veins A hidden infection as a source of antigen was considered and 250 mg tetracycline every six hours was given Pyrexia subsided slowly and abdominal symptoms disappeared Tetracycline was discontinued two weeks after temperature became normal Weight gain was rapid and the patient has been in good health since discharge

The lesion was essentially a form of granulomatous phlebitis with epithelioid tubercle formation occurring in a small vein Special stains did not reveal any organisms and the more usual causes of epithelioid cell reaction (tuberculosis syphilis brucellosis histoplasmosis) appeared to be ruled out A syndrome of febrile primary phlebitis with vein lesions regarded as identical with those in this case was recently reported by the Chakravartis as a case of giant cell polyphlebitis [Brit M J 1 253 Jan 29 1955 —Ed]

Sicca Syndrome Gougerot Sjogren Disease Frequent references to Sjogren s disease appear in the European medical literature Such reports however are rare in American journals and are confined chiefly to the field of ophthalmology It is believed that this syndrome is a manifestation of systemic disease Keratoconjunctivitis sicca rhinitis sicca pharyngitis sicca xerostomia and swelling of the parotid glands are cardinal features In addition rheumatoid arthritis caries accelerated sedimentation rate achylia gastrica diminished perspiration dryness of the vulva and vagina altered glucose tolerance curve hypo

(1) I h J M S Pp 129 134 M 1

The Bamberger Marie syndrome when fully established is characterized by new periosteal growth of long bones increased size of extremities clubbing of fingers and toes and redundancy of the skin of face and skull Joints may be swollen and deformed Pulmonary malignancy occasionally is associated with this acromegalic type or it may accompany a form of arthritis clinically indistinguishable from rheumatoid arthritis Peripheral neuritis and phlebothrombosis of the extremities may also be associated with pulmonary malignancy

Association of dermatomyositis with malignancy was first reported by Bezecny in 1935 and 35 cases have now been reported Lansbury adds six cases of collagen disease (dermatomyositis disseminated lupus erythematosus and arthritis) complicating respectively carcinoma of the kidney malignant seminoma carcinoma of the esophagus and Krukenberg tumor of the colon in all of which malignancy preceded dyscollagenoses

In dermatomyositis there is no relation to type or site of origin of the malignancy Conversely there does seem to be some relation between bronchogenic carcinoma and the Bamberger Marie syndrome In many cases connective tissue manifestations were completely and permanently reversed by excision of the tumor Although connective tissue reactions have been classified as arthritis dermatomyositis disseminated lupus erythematosus and Bamberger Marie syndrome there seems to be considerable overlapping in their features since collagen diseases tend to present a pleomorphic clinical picture

The mechanism by which malignancy and connective tissue disorders are related is unknown Current speculations include infection allergy hormones metabolism and neurologic reflexes Occurrence of either the Bamberger Marie syndrome or of any of the dyscollagenoses in a middle aged patient calls for a meticulous clinical radiographic and endoscopic study for detection of an early operable malignancy

[The association of dermatomyositis and neoplastic disease is so common that special search for carcinoma should be carried out in any patient seen with dermatomyositis The Bamberger Marie syndrome is better known as hypertrophic pulmonary osteoarthropathy Its relation to pulmonary carcinoma is intriguing surgeons report that the arthritic symp

toms may be strikingly relieved within 24 hours after removal of a bronchogenic carcinoma —Ed]

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(1) I h J M S pp 129 134 M h 1955

chronic anemia alopecia Raynaud phenomena and scleroderma have been described Mikulicz disease uveoparotitis (Heerfordt) of sarcoidosis lymphomas and mumps must be considered in differential diagnosis Joseph C Ehrlich and David Greenberg (Lebanon Hosp New York City) report a case

Woman 49 developed signs and symptoms of arthritis three years before hospitalization A year later she noted dryness of the lips and mouth and a sensation of burning and dryness of the eyes with inability to make tears She lost 20 lbs and began to lose her teeth Bilateral irregular enlargement of the parotid glands soon followed. After hospitalization she was started on 100 mg cortisone daily later decreased to 25 mg /day Under therapy she gained weight and there was regression of parotid swelling diminution in dryness of the mouth and to a lesser degree of the eyes

The proper status of this disease with respect to Mikulicz disease is unclear Mikulicz disease has been redefined as a benign chronic condition predominately of women of the fifth and sixth decades which almost always involves one or more salivary glands and less often the lacrimal glands Grossly there is preservation of the normal architecture with diffuse enlargement microscopically there is replacement of the acinar parenchyma by lymphoid tissue and an intraductal proliferation of epithelial and myoepithelial cells The similarity to Gougerot Sjogren disease is so striking that several writers have undertaken reinvestigation of their entire material to explore further the inter relation Despite conflicting reports it appears established that atrophy and disappearance of secreting parenchyma occur in both Mikulicz and Gougerot Sjogren disease and it would not be surprising therefore if clinical evidence of loss of secretion is also shared Several authors have suspected cross diagnosis of the conditions Whether or not the extraocular manifestations known to be associated with keratoconjunctivitis sicca may also occur with significant frequency in Mikulicz disease await further analysis of clinical data

[Sicca syndrome is perhaps more descriptive and easier to remember but Sjogren's syndrome seems to have a head start. It may be identical with Mikulicz disease Cases will probably be recognized more frequently in America now that descriptions are beginning to appear in our medical literature We have seen two cases in New Haven in the past year —Ed]

(2) A.M.A Arch Int Med 93 731 743 May 1954

Wegener s Granulomatosis may be recognized clinically by combination of severe sinusitis or pulmonary inflammation variable symptoms of arteritis and terminal renal insufficiency At least 18 cases with autopsy reports have been published John L Fahey Edward Leonard Jacob Churg and Gabriel Godman[3] present seven new cases in six autopsy was done and one patient was still living and under treatment

In four cases the upper respiratory passages (nose paranasal sinuses nasopharynx glottis or epiglottis) were involved in destructive necrotizing granulomatosis In all cases necrotizing giant cell granulomas were present in lungs and bronchi In the kidneys examined at autopsy focal necrotizing thrombotic glomerulitis more or less widespread was the rule In all autopsies splenic lesions ranging from small foci of necrosis to total infarction and apparently dependent on unusually widespread trabecular and follicular arteritis were found and in some scattered granulomas were also encountered Infarcts hemorrhages thromboses and aneurysms were found in the lungs in all and in the kidneys in five Vascular lesions in heart gastrointestinal tract adrenals testes and pancreas occurred less frequently

Diagnosis of Wegener s granulomatosis may be suggested by persistent respiratory tract inflammatory lesions of unknown cause especially if accompanied by signs of renal damage or by arteritis with granulomas in one or several sites The disease affects previously healthy men and women of all ages most frequently in the fourth and fifth decades generally without history of allergy asthma or exposure to sulfonamides Duration is brief six months on the average and the outcome fatal

Persistent sinusitis or rhinitis severe enough to cause ulceration and bony or cartilaginous destruction may be the first symptom Any part of the lung may be involved In many cases constitutional symptoms are out of proportion to the intensity of the local process and the patient seeks help because of weakness fever or progressive weight loss Whatever the local lesion it seldom responds to usual therapy Sinusitis persists despite drain

(3) Am. J M d 17 168-179 A gu t, 1954

age and chemotherapy pulmonary lesions progress far enough to require surgery Episodes often transient of arthritis neuritis carditis parotitis and prostatitis have been seen Extensive studies fail to implicate any specific micro organism and antibiotics apparently only help control secondary infection

ACTH and cortisone apparently controlled systemic symptoms and inflammatory lesions in one patient but this case is somewhat atypical because of prolonged subacute course No other drugs are known to be effective though nitrogen mustards deserve further study

Other conditions to be differentiated include (1) specific infectious granulomatous disease (2) Boeck s sarcoid (3) progressive destruction of upper air passages (granuloma gangrenescens) (4) periarteritis nodosa (Wegener s granulomatosis has sometimes been considered a respiratory-renal subtype) and (5) allergy (asthma eosinophilia) i e allergic angiitis

[Here is another distinctive syndrome we should be aware of Perhaps the features to be kept in mind can be summarized as intractable sinusitis indolent pulmonary lesions renal vascular disease and continued fever —Ed]

Effect of Cortisone in Polymyositis Report of Two Cases is presented by Bengt Skanse[4] (Malmo Sweden) Polymyositis is a rare disease with skeletal muscles the sites of nonsuppurative usually chronic inflammation Muscle weakness may be so extreme as to simulate muscle paralysis affected muscles are sore and swollen and subcutaneous edema may be prominent especially in the eyelids Firmness on palpation tenderness on pressure and pain of involved muscles on motion are usually pronounced although joints are rarely affected Generally considered a distinct clinical entity polymyositis has much in common with dermatomyositis and may be one form of it even though skin involvement is absent The involved muscles show interstitial edema focal degeneration perivascular inflammation and eventually fibrosis Histologic changes are similar perhaps identical in the two diseases The clinical course varies Prolonged spontaneous remissions occur but usually prognosis is poor

Although ACTH and cortisone have been used by oth-

(4) Acta med scandinav 150 169 174 1954

ers in treatment of dermatomyositis the following cases are apparently the first reported of use of cortisone in polymyositis

CASE 1 —Woman 27 critically ill with profound muscular weakness had distressed breathing and difficulty in swallowing Cortisone produced dramatic initial improvement but not complete remission Therapy was continued for a year any attempts at discontinuance during this period resulting in recurrence of symptoms After termination of treatment she remained well for 10 months and had no recurrence of symptoms except stiffness and slight pain in the fingers

CASE 2 —Woman 32 ill with chronic polymyositis for many years also had mild psoriasis recurrent parotitis and dryness of conjunctival and oral mucosa After an exacerbation treatment with cortisone caused improvement but no definite remission She had been treated for 1½ years and several attempts to withdraw the drug had resulted in increased muscular weakness Relation between polymyositis and keratoconjunctivitis sicca dry mouth and recurrent parotitis remained unclear

[The second case has features suggestive of Sjogren s syndrome (this YEAR BOOK p 101) These are examples of a poorly understood group, perhaps belonging somewhere in the spectrum of the collagen diseases' It is not surpri ing that corti one suppressed the manifestations but did not have a curative effect —Ed]

FEVER

Initial Process in Action of Bacterial Pyrogens in Man which involves a latent period of over 45 minutes after intravenous injection preceding pyrexial reaction is at present obscure Animal experiments indicated that onset of fever was accelerated if the pyrogen was first incubated with blood serum or plasma J Gerbrandy W I Cranston and E S Snell[5] (St Mary s Hosp Med School London) attempted to confirm this finding in man

PROCEDURE —Oral and rectal temperatures were measured at one minute intervals with copper constantan thermocouples In 11 subjects a killed Bacterium coli preparation was given in doses of 5 20 million organisms Two subjects received a polysaccharide preparation fractionated from a strain of pseudomonas in doses of 40 and 80 µg No qualitative difference between results with these preparations was observed All subjects received an intravenous infusion of their own blood incubated with pyrogen except one who received the pyrogen in blood from a compatible donor All acted as their own controls receiving the same dose of pyrogen from the same batch

(5) Cl S 13 453 459 N mb 1954

in different ways except for one who received 80 μg piromen as a control and 40 μg as the test infusion

The results showed that when pyrogen was incubated with fresh blood before intravenous injection, the fever began significantly earlier than when pyrogen was given alone (Fig 17) Thus it seems that the delay normally occurring between injection of pyrogen and onset of fever

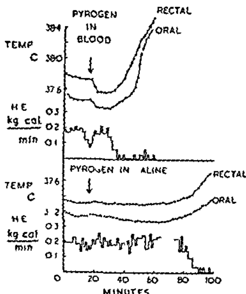


Fig 17 —Upper chart shows response to 15 million B coli pyrogen units incubated in 250 ml blood on 20 8 53 lower response to 15 million in 10 ml saline on 17 8 53 (Courtesy of Gerbrandy J et al Clin Sc 13 453-459 November 1954)

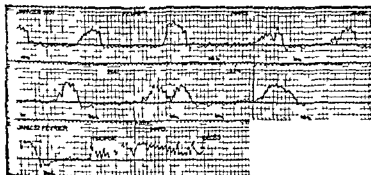
may be largely accounted for by a reaction between the pyrogen and a constituent of blood

[The latent period between injection of a bacterial suspension and onset of fever has always been difficult to explain In practice a similar interval of about an hour is likely to elapse between instrumentation of an infected urethra transient bacteremia and resulting chill The study reported here seems to shed some light on the sequence of events —Ed]

Malignant Reticulopathy with Repeated Cyclic Recurrence of Fever In 1950 Mollaret Bertrand and Mollaret reported a strange case of periodic bimonthly fever with lesions of reticulosis and in 1953 R Crosnier and co workers encountered another case of malignant reticulosis

in which the fever chart presented the same bimonthly periodicity throughout 15 months R Mazaud and D M Luigi[6] (Marseille) describe a case of a similar febrile syndrome in which the pathologic lesions apparently were of a type intermediate between those in the two previous cases

Man 36 had recurrent fever which had begun in September 1950 four months after he returned to France after 27 months army service in Indochina While there he had had intestinal amebiasis and suspected marsh fever He was also an alcoholic The fever peaks (Fig 18) maintained a consistent pattern Phases lasted six or sev



F g 18 – T mpe u (C rt y f M a d R d L g D M P se m d 6 670 671 Ap 8 19 4)

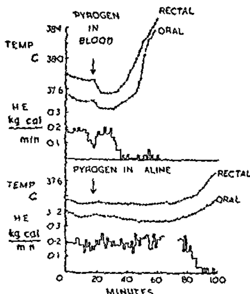
en days and then recurred almost always after 21 days Subjective 1
symptoms were profound weakness which appeared the day before slight chills during the temperature rise moderate headache and then abundant sweating *during the febrile recession and the period of* hypothermia which lasted 24-48 hours afterward there was no pruritus During the intervals when temperature was normal he seemed well and was quite active Loss of weight was moderate and progressive Liver was hypertrophic consistent with the alcoholism

An acute pulmonary episode occurred during the febrile phase of Feb 11 1951 with condensation of the right apex producing a triangular shadow on the roentgenogram which disappeared after a few days The second episode during a febrile recurrence (Jan 26 1952) appeared to be acute bilateral pneumonopathy worse on the right with x ray signs of bronchopneumonia which again cleared promptly By February 7 there remained only a fine network with some micronodules of increased density At the time of this acute pulmonary complication leukocytes increased to 13 000 with 65%

(6) P esse m d 6 670 671 Ap 28 1954

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F g 17—Upp r ch rt bow re pons to 15 m llion B oli org n s s incu bat d n *50 ml blood n 20 8 53 lowe esp n e to 15 m ll on n 10 ml al e on* 17 8 53 (Courtesy of Ge brandy J et al Cl n Sc 13 453-459 N vembe 1954)

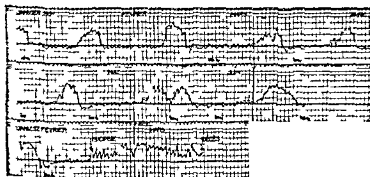
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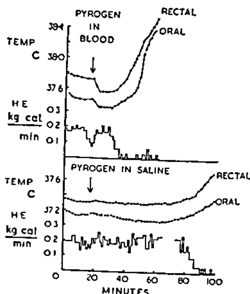
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rate declined except for a light rise in 1943-46 and in the past three years there were only six deaths one due to pseudomonas infection Since 1941 postoperative generalized peritonitis has become rarer from year to year so that surgeons are no longer greatly concerned about this complication even with extensive one stage operations From 1927 to 1941 in 2 556 consecutive autopsies 17 deaths were attributed to perforative appendicitis and generalized peritonitis about half the patients were over 50 and none received antibiotics In 2 434 autopsies during 1941 52 only two deaths were due to perforative appendicitis and generalized peritonitis in neither case were antibiotics given In the first 2 000 autopsies in 1927-41 there were 59 instances of vegetative endocarditis in the second 2 000 37 Among 104 autopsies on obstetric patients in 1927-41 serious infection was the dominant cause of death in 48 case Since 1941 only 6 of 80 autopsies have revealed dominating infection

Despite the spectacular accomplishments of antibiotic therapy new problems have arisen e g appearance of resistant bacterial strains superimposed infections presumably activated by alterations in bacterial ecology and drug reactions However it would be unfortunate to overemphasize their importance and minimize the gains of treatment The complication of greatest current interest is superimposed infection resulting from suppression of drug sensitive organisms and concomitant emergence of drug resistant strains—fungi staphylococci pseudomonas and proteus Though not usually highly pathogenic these organisms seem as a result of antibiotic action to find tissues more favorable for growth and to be responsible at times for generalized or terminal infection There is increasing evidence of a rising incidence of staphylococcic infections such as wound infections bacteremia pyemia endocarditis and bone infection Evidence is lacking that antibiotic resistant staphylococci themselves have become more pathogenic It seems rather that their normally competitive environment has been interfered with so they are no longer subjected to the usual bacterial antagonisms

Man made diseases will presumably continue so long as chemists provide new therapeutic compound In the mean

polymorphonuclear neutrophils 10% polyeosinophilic mononuclears and 25% lymphocytes The hemogram had been normal previously Repeated cultures and laboratory studies revealed no evidence of bacterial or parasitic infection and no toxic, nutritional or metabolic factors were found to account for the illness Bone marrow studies showed nothing abnormal

After the second pulmonary attack patient's general state deteriorated anemia progressed and bilirubinemia appeared Hepatomegaly increased with ascites significant splenomegaly and polymicroadenopathy of inguinal axillary and cervical nodes Since repeated blood transfusions did not halt the anemia or leukopenia radiotherapy was given He died a month later with signs of functional intestinal obstruction

Biopsy of an inguinal node removed during a febrile attack showed diffuse metaplasia of the reticuloendothelial system corresponding to the histiomonocytic reticulosis of amonocytemic type described by Cazal Sections from the liver disclosed lobular fatty degeneration with numerous histiocytic foci

[The curious periodicity of fever in a variety of diseases affecting the hemopoietic system has excited much speculation but the mechanism is still mysterious The picture presented by this patient would fit with some of those in the group of disorders called periodic disease by Reimann (Medicine 30 219 1951) —Ed]

MISCELLANEOUS SUBJECTS

Changing Pathologic Picture of Infection since Introduction of Chemotherapy and Antibiotics is discussed by Paul R Cannon (Univ of Chicago) Some frequently lethal diseases e g lobar pneumonia purulent meningitis mastoiditis puerperal sepsis septicopyemia venereal disease and others have been virtually eliminated as a cause of death A 25 year review of autopsies beginning in 1927 showed the autopsy rate relatively unchanged (70 80%) A reasonable continuity has been maintained in procedures and terminology

Among 2 000 consecutive autopsies to 1940 lobar pneumonia was the principal cause of death in 50 cases since 1940 in another 2 000 autopsies only seven deaths were attributed to this disease and during the past few years none In earlier years when otitis media and mastoiditis were common deaths from meningitis were numerous From 1927 to 1941 in 2 000 autopsies 61 deaths were ascribed to purulent meningitis Since 1941 the fatality

(7) Bull New York Acad Med 31 8 10 Feb 1955

most forms of pneumonia the drug of choice initially is penicillin

[The author makes a good point bronchitis or pneumonia may be as common and important as thromboembolic disease among the complications of heart failure —Ed]

Studies on Recurrent Aphthae Evidence that Herpes Simplex Is Not the Etiologic Agent with Further Observations on Immune Responses in Herpetic Infections is presented by Marvin M Stark Sidney Kibrick and David Weisberger[9] (Boston) since a relation between recurrent aphthae and herpes simplex is thought by many to exist and has been both supported and rejected by clinical and laboratory studies

Primary infection with herpes simplex virus may take several clinical forms such as vulvovaginitis or meningoencephalitis but the commonest is that with intraoral manifestations Acute herpetic gingivostomatitis is characterized by fever foul breath gingival inflammation a transitory vesicular eruption in the oral mucosa and submaxillary adenopathy Biopsies characteristically show a ballooning degeneration of epithelial cells multinucleate giant cells and intranuclear inclusion bodies in the affected cells Since the virus is widely disseminated primary exposure is likely early in life

Unlike primary herpes lesions which are usually multiple appear over a short period and often coalesce recurrent aphthae (recurrent aphthous ulcers canker sores recurrent aphthous stomatitis) are usually solitary lesions In over 100 cases the sites were in order of frequency the buccal mucosa buccal sulcus lateral margin of tongue mucosal surface of lips floor of mouth soft palate and gingivae Early there is usually a small localized oval area of redness Adjacent tissue is not involved A superficial yellow to grayish membrane rapidly develops and may be surrounded by a fine zone of erythema but vesicle formation has not been observed Pain may be so severe that nutrition is impaired In two or three days a superficial slough occurs leaving a shallow ulcer the base of which is soon covered by grayish granulation tissue After one to six weeks the ulcer heals with or without scarring The lesions show no characteristic histology

(9) J L b & Cl M d 44 261 272 A g t 1954

time pathologists must study their effects on living tissues which it is hoped will continue to constitute mostly minor problems

[Cannon's analysis of experience in one medical center before and after the antibiotic era provides some good factual information to bolster clinical impressions.—Ed.]

Factor of Infection in Heart Failure is stressed by F J Flint[8] in a review of 300 patients with congestive heart failure (159 males and 141 females) admitted consecutively to the City General Hospital Sheffield between March 17 1952 and March 16 1953 Over half (167) had some form of respiratory infection In 156 there was evidence that this was the precipitating cause of failure (bronchitis in 103 pneumonia in 51 tuberculosis in 2) and in only 11 most of whom were comatose was it thought to be secondary Heart failure was precipitated by a respiratory infection in 74 of 76 patients with cor pulmonale and in 62 of the remaining 224 with other forms of heart disease Incidence of heart failure in winter was twice that in summer Postmortem examination was performed in 88 cases death was due to pneumonia in 21 and to acute bronchitis in 17

It has long been accepted that congestive heart failure in patients with cor pulmonale is precipitated by a respiratory infection In those with heart failure due to ischemic heart disease hypertension rheumatism and other causes however hypoxia and hypercapnia are slight compared with the gaseous disturbance in cor pulmonale In these, there are at least two possible explanations for precipitation of heart failure by respiratory infection (1) with left heart failure or mitral stenosis resulting pulmonary congestion causes pulmonary edema providing an excellent medium for growth of bacteria even of low virulence (2) infection may directly or indirectly damage the myocardium and thus lead to cardiac failure especially in persons with pre existing heart disease

In many cases of heart failure particularly those occurring in winter chemotherapy is probably more important than any other item of treatment including digitalis or mersalyl Further work is in progress to discover which antibiotic is most useful for treatment of bronchitis For

(8) Brit. M. J 2 1018 1022 Oct. 30 1954

due to pooling in the lumbar area and did not indicate the level in the cisternal region

Good functional recovery is the rule When bulbar manifestations prevail death may ensue from involvement of the vital centers Recovery may be slow but is usually continuous Recovery of function descends so the first parts involved usually the legs are the last to recover Treatment consists of hydrotherapy stretching of tight structures and splinting to prevent deformities

Differentiation of this disease from poliomyelitis is important Unlike poliomyelitis the etiology is unknown In poliomyelitis there are fever systemic infection and rapid onset of paralysis Meningeal irritation headaches and vasomotor changes are rare in Guillain Barre disease whereas they are frequent in poliomyelitis Sensory changes are rare in poliomyelitis but frequent in Guillain Barre disease The motor symptoms are bilateral symmetrical and *ascending* and *paralysis may progress for days or weeks* whereas paralysis in poliomyelitis follows no pattern is spotty and additional involvement rarely occurs after the second week Optic neuritis is not infrequent in both diseases as well as diplopia and involvement of the 9th and 10th cranial nerves However facial paralysis is frequent in Guillain Barre disease as high as 50% of the cases in some series The spinal fluid in this disease reveals high total protein with few cells there are many cells and only slightly elevated total protein in poliomyelitis *With extensive involvement the prognosis in poliomyelitis* is poor whereas in Guillain Barre disease the chance for functional recovery is good

Paralysis Due to Bite of a Tick Jack Chesney (Knoxville) states that tick paralysis may be mild consisting of slight weakness of the legs with ataxia or may be an ascending flaccid paralysis If the tick is not removed the disease progresses to bulbar paralysis and death

Girl 5 stumbled when she walked and a day later became ataxic and could not walk or stand alone A mass of moderately enlarged posterior cervical suboccipital lymph nodes was present on the right side Cerebrospinal fluid was clear with normal pressure sugar chloride and protein content ulture and smear were negative for organisms The third dav an engorged tick was found embedded in

( ) J T M A 48 77 80 M h 195

Although in many patients food allergy was suggested as the cause of recurrent aphthae elimination diets skin tests and antihistamines had no consistent effect on frequency of recurrences Smallpox vaccination tried in about 50 patients with severe forms also had no effect Correction of vitamin deficiencies and empiric use of large doses of vitamins were of no value

To re evaluate the role of herpes virus in recurrent aphthae complement fixation and/or virus neutralization tests were done on 101 serums from 62 subjects with histories of recurrent aphthae herpes infection or both Incidence of herpes complement fixing antibodies was not increased in subjects with recurrent aphthae compared with controls Of 30 with recurrent aphthae 11 had no demonstrable antibodies Skin tests were done on 7 of the 11 and 5 failed to react The same seven patients had recurrences during the study and none showed a rise in herpes antibodies during convalescence These findings and the fact that recurrent aphthae lesions are pathologically inconsistent with herpetic infection make a herpetic etiology for this disorder unlikely

[Apparently a well conducted investigation leaving this annoying disorder more puzzling than ever —Ed]

Guillain Barre Syndrome Richard D Mulroy[1] (New York State Rehabilitation Hosp West Haverstraw) describes 12 patients whose histories and clinical and laboratory findings were compatible with the diagnosis of Guillain Barre syndrome In half the patients infection usually of the upper respiratory tract preceded the disease process Frequently there was a latent period then sudden onset of neurologic signs either sensory or motor Usually the motor weakness started in the feet and ascended If sensory effects preceded the motor paresthesias and hyperesthesias of the hands and feet were noted The sensory phenomena however were often overshadowed by ascending flaccid paralysis that followed Cranial nerve involvement was common Laboratory findings were normal and did not suggest infection Cerebrospinal fluid was diagnostic in that the cell count was usually below 25 and total protein above 45 mg Increased total protein was thought

(1) New York J Med. 54 1761 1764 June 15 1954

about 75% in one day and disappeared entirely in three days One week later painful swelling of the thyroid returned and ACTH gel was again administered but for one day less A second relapse within 10 days was treated by ACTH for two days On a third relapse 60 units and on a fourth 80 units were given in one injection each Response to the hormone was rapid and complete in each instance Patient made an uneventful recovery

CASE 2—Woman 44 had had a painful swollen neck for about six weeks A tender hard nodule about 2 cm in diameter was present in the right lobe of the thyroid and the remainder of the gland was slightly enlarged Symptoms were relieved within 12 hours after she received the first dose of corticotropin gel (80 units) and the nodule decreased to about half its former size It disappeared completely within eight days After three days dosage of ACTH was reduced to 60 units for two days then 40 units and finally 20 units for two days Examination six months later revealed no signs of thyroiditis In this case corticotropin served as an important aid in ruling out carcinoma of the thyroid

[There is little evidence that this disorder is infectious ACTH seems effective in controlling symptoms and appears to be the best treatment available —Ed]

Intravenous Injection of Bovine Crystalline Pancreatic Desoxyribonuclease into Patients formed part of a comparative study by Alan J Johnson Pauline R Goger and William S Tillett[4] (New York Univ) on streptococcic desoxyribonuclease contained in varidase® *Observations* were made on renal excretion and clearance of the pancreatic desoxyribonuclease (PD) its diffusion into various extravascular areas and the effect of intrathecal injections on adults and children with and without meningitis Extensive clinical and laboratory examinations were made for evidence of toxicity

PD was injected intravenously in 65 adults and 45 children in doses successively increased from 10 to 2 000 000 units/injection There was no evidence of systemic toxicity of PD by any parenteral route Special attention was given to rate of injection to prevent nonspecific foreign protein reaction Injection time varied from two minutes to several hours at each dosage level No reactions occurred

Since it has been suggested that the L E cell phenomenon may be potentiated by increased serum desoxyribonuclease or destruction of an intracellular inhibitor L E cell preparations were carried out at various intervals after

(4) J Cl n I t 33 1670 1686 D mbe 1954

the scalp in the upper right occipital region The tick was removed Later that day the child was able to walk with slight help and the next morning walked without difficulty Lymphadenopathy subsided rapidly

It is believed that the toxin is formed by a female tick who is maturing her eggs and that it is largely concentrated in the eggs some toxin is contained in the saliva of the gravid tick For paralysis to develop it is almost certain that the tick must be a gravid female and that it must be attached to the person five to eight days The bite of a male tick probably never causes paralysis Many types of ticks are known to cause paralysis cases in the Northwest are associated with Dermacentor andersoni (wood tick) and those in the East primarily with D variabilis

Tick paralysis should be kept in mind when children with weakness ataxia or paralysis are seen in the summer months When found the tick should be removed as a whole without leaving mouth parts in the skin Ether acetone or benzene will loosen it in about 10 minutes Gentle straight traction is better than twisting motion Improvement usually follows within a few hours

[Cases have appeared in all parts of the country nearly always in girls the tick being concealed by the hair We ought to try always to remember to look for a tick in the scalp of a girl suspected of having poliomyelitis —Ed]

Treatment of Subacute Thyroiditis with Corticotropin in two cases is reported by Milton Cutler[3] (Hammonton N J) The cause of subacute nonsuppurative thyroiditis also called pseudotuberculous or giant cell thyroiditis is unknown It is characterized by a painful tender firm usually diffuse enlargement of the thyroid with fever pain on swallowing hyperthyroidism (at least in the beginning) elevated sedimentation rate and polymorphonuclear leukocytosis It runs a variable course for weeks or months and eventually subsides

CASE 1 —Woman 67 had a painful tender swelling of the neck and had had generalized weakness for a month The condition had become progressively worse despite treatment with propylthiouracil Thyroid was enlarged tender and hard Corticotropin gel was given intramuscularly 40 units daily for four days and 20 units the fifth day Within eight hours after the first dose pain and tenderness disappeared Weakness decreased rapidly and swelling was reduced

(3) J.A.M.A. 155 650-651 June 12 1954

jections during 1½ months The other received over 11 000 000 units in 24 intravenous injections and nearly 3 000 000 units in 24 lumbar and 20 intraventricular injections No toxicity was evident in either child

Blood level of PD an hour after single injections of 1 000 000 units to 20 patients averaged 30 units/ml (range 18 50)

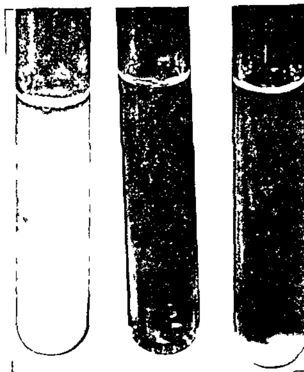
Large amounts of PD were excreted in the urine without demonstrable proteinuria or hematuria When 10 000 1 000 000 units was given in 30 minutes or less 5 10% was regularly recovered in the urine When the same dose was given over four hours as much as 20% was excreted Therefore 1 000 000 units was given intravenously (without antibiotic) to a woman 86 with profoundly purulent urine owing to cystitis (Fig 19) The striking effect was/ transitory exudate beginning to reappear in 24 hours

PD injected intravenously diffused readily into peritoneal and pleural fluids wound exudates and bronchial secretions Three patients with tuberculous meningitis with cerebrospinal block were given intravenous and intrathecal injections of PD In two the block was relieved A patient with ascites given a single injection of 1 000 000 units showed an abrupt rise and fall of level of PD in the serum paralleled by a similar but lesser rise and fall in ascitic fluid In tuberculous pleural effusion intravenous injection of 1 000 000 units of PD resulted in a ri e and then a fall in serum level with a similar rise of PD in pleural fluid Level of PD in edema fluid obtained by Southey tubes inserted into the legs of a patient with cardiac failure started to rise about a half hour after rapid intravenous injection of 1 000 000 units

Dose of PD may have to be increased or repeated oftener to obtain maximal depolymerization of purulent material in sputum Respiratory mucin exerts a protective action on the desoxyribonucleoprotein in sputum and excessive amounts of mucin may limit effectiveness of PD excreted into the bronchial area In 23 cases of uncomplicated purulent bronchitis 2 5 mg crystalline PD in gelatin buffer by inhalation induced striking but transitory reduction in viscosity of purulent sputum lasting about 12 hours When the purulent sputum had already become mucoid

injection of 1 000 000 units of PD No evidence of L E cell transformation was found in these in vivo studies

Intrathecal injections of 10 50 000 units/injection were given normal persons and patients with meningitis Repeated intrathecal injections (50 000 100 000 units injec



F g 19 —U mpl t k befo e d a d 24 h ft j t t
PD (C t y f J h A J t l J (l n 1 t 33 1670 1686 D cember 1954)

tion) were given 15 patients with pyogenic and 3 with tuberculous meningitis without toxic reactions The pyogenic meningitides included three cases due to Hemophilus influenzae three to Diplococcus pneumoniae seven to meningococcus and two to Staphylococcus aureus Of two children with tuberculous meningitis one received about 23 000 000 units in 27 intravenous injections and 2 000 000 units in 18 lumbar (intrathecal) and 25 intraventricular in

jections during 1½ months The other received over 11 000 000 units in 24 intravenous injections and nearly 3 000 000 units in 24 lumbar and 20 intraventricular injections No toxicity was evident in either child

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no change in viscosity followed inhalation of PD Thus a respiratory mucinase should be used with PD in cases with highly viscous respiratory mucin

The crystalline enzyme used in these studies is a relatively poor antigen in man when injected intravenously or intrathecally Since PD exhibits the unusual capacity of renal excretion and of diffusion into various extravascular areas local sites of disease not easily accessible for topical application may be reached via the intravenous route

[The field of usefulness for this material should be comparable to that of the streptococcic desoxyribonucl ase (varidase®) The lack of unpleasant side effects noted by these workers is encouraging —Ed]

The Chest

CARL MUSCHENHEIM M D

PART II

THE CHEST

PHYSIOLOGY

A field of physiology which has come into clinical prominence particularly in the past year is that concerned with the mechanics and efficiency of breathing which is referred to by the general title The Work of Breathing For an understanding of the fundamental concepts and methods the reader is referred to a review under this title by A B Otis (Physiol Rev 34 449 1954) and to a presidential address by R V Christie entitled Dyspnea in Relation to the Visco elastic Properties of the Lung (Proc Roy Soc Med 46 381 1953) An interesting discussion of some of the therapeutic implications will be found in an editorial on the subject by R. L. Riley (Ann Int. Med 41 172 1954)

Several of the most significant relations to arise from this field of investigation are (1) the relation of optimal respiratory frequency to minimal work of breathing (see Marshall and Christie below) (2) the relationship of dyspnea to the force exerted on the lung (see Marshall Stone and Christie p 124) and to the energy required (see Cournand *et al* p 125) and (3) the relation of the work of breathing to respiratory acidosis In analyzing this last relationship Riley (op cit) has made the surprising deduction that in emphysematous patients the work of breathing may be more tolerable at an elevated arterial CO_2 tension and that respiratory acidosis may therefore be viewed as an adaptive mechanism —Ed

Viscoelastic Properties of Lungs in Acute Pneumonia

Simultaneous recordings of intraesophageal pressure and air flow or tidal volume were made by R Marshall and R V Christie[1] (St Bartholomew s Hosp London) From the pressure flow or pressure volume tracings obtained coefficients of elastic resistance and of viscous and turbulent resistance were calculated and the work of breathing was calculated from pressure volume diagrams When flow tracings were not made it was not possible to calculate the coefficients of viscous and turbulent resistance At low rates of air flow it is difficult to divide nonelastic resistance into its viscous and turbulent components by the method of residuals This accounts for the apparent large increase in turbulent resistance and reduction in viscous resistance in many instances (table) The unequal division has little effect on the work of breathing at different frequencies

In all but one case there was considerable increase in the

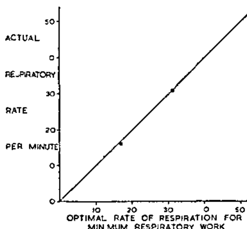
(1) Cl Sc 13 403 408 A g t 1954

Results in Seven Patients with Acute Pneumonia

Patient	Date	Force Exerted cm H O	Coeff elastic r s st cm H 0/ l	Co ff sco s re st cm H 0/l/sec	Coeff tu bule t esi t cm H-0 (l/sec)²	Tidal vol me ml	Minute olume l tres	Resp rate	Opt mal resp rate
J R	9 8 53	13 4	8 0	0 83	1 16	485	5 4	52 4	46
	17 8 53	1 0	18 4	6 33	0	530	14 6	7 6	5
	5 10 53	9 0	11 8	7 40	0	833	13 4	16	17
E. H	14 9 53	7 6	9 5	1 81	1 8	750	12 9	17 2	21
	6.3 54	9 4	6 8	—	—	1097	15 4	14 2	—
J M	8 12 53	10 2	15 4	—	—	679	25 2	37 1	—
"	30 12 53	8 4	8 2	—	—	838	17 2	0 5	—
T C	5 1 54	12 4	24 9	2 6	0	355	11 6	37 6	30
W S	1 1 54	13 3	25 6	3 6	0	527	19 7	37 4	36
	14 1 4	13 5	15 2	—	—	866	16 5	19 0	—
	1 1 54	7 9	8 4	0 77	0 83	715	18 0	25 2	30
F A	6 1 54	1 8	18 0	4 27	0	710	4	31 6	34
"	2.2 54	11 4	13 8	—	—	8	10 7	13 0	—
"	10 54	10 1	12 1	—	—	775	18 6	40	—
"	17 2 54	12 3	13 2	—	—	778	9 3	12 0	—
	25.2.54	9 7	10 2	1 02	3 74	940	1 2	13 0	18
E. D	4 3 54	14 1	19 2	0 28	3 83	724	22 5	31 1	31
"	6 3 54	17 4	23 7	—	—	719	14 4	01	—

coefficient of elastic resistance in the acute stage of the disease After recovery lung rigidity fell to within normal limits of 4 3 10 5 cm H O/L Coefficients of nonelastic re sistance showed wide variations and there was no signifi cant difference between values obtained in the acute stage of the disease and after recovery The force exerted shown in the table is the total change in intraesophageal pres sure on inspiration

The increase in lung rigidity demonstrated in these cases



F g 20 —R lat h p pneumon betw act l p t y t d t at wh h p t ry work m n m l (C t y f M h ll R d Ch t R. V Cl S 13 403-408 A g t 1954)

cannot be explained by changes in the consolidated areas only Normal lungs show a linear relationship between tension and volume increase up to a tidal volume of about 2 L so that in a patient with pneumonia one would not expect any increase in the coefficient of elastic resistance with breaths of less than 1 L even if one whole lung were to be consolidated provided the other lung remained nor mal

In the patients studied there was no relation between amount of consolidation shown by x ray and coefficient of elastic resistance For example in patient W S (table) the coefficient of elastic resistance fell from 25 6 cm H O/L

to 15 2 cm but chest x rays showed no change in amount of consolidation

Increase in lung rigidity in acute pneumonia must be due to increase in rigidity of the unconsolidated and apparently normal areas of the lung It is unlikely that shunting of blood through these areas could cause this rigidity for no increase occurs in normal subjects on exercise or in patients who have a patent ductus arteriosus with a high pulmonary blood flow Nor is fever alone the cause Probably the increase is due to generalized congestion of the lungs

Rapid respiration in acute pneumonia was hitherto unsatisfactorily explained The optimal rates of respiration for minimal respiratory work in six patients are shown in Figure 20 The rapid breathing characteristic of acute pneumonia is most economical in terms of respiratory work

Relationship of Dyspnea to Respiratory Effort in Normal Subjects Mitral Stenosis and Emphysema Recent investigations have shown that the rate of doing respiratory work on exercise is increased in patients with mitral stenosis or emphysema and it was suggested that this increase might be partly responsible for making the patient conscious of respiratory effort In investigating the relation between dyspnea and the work of breathing R Marshall R W Stone and R V Christie (St Bartholomew s Hosp London) found that the only sensation they could assess accurately was that the limit of respiratory performance had been reached and that any further increase in ventilation would be extremely unpleasant or impossible To obtain a repeatable end point patients were exercised at a rate that produced arresting shortness of breath in six minutes

The intraesophageal pressure was measured by an air filled polythene tube connected to a capacitance manometer and tidal volume by a pneumotachograph and resistance capacitor integrator From the tracings of intraesophageal pressure and tidal volume pressure volume diagrams were constructed from which the work of breathing could be calculated Measurements were made on 8 normal subjects 8 patients with mitral stenosis and 10 with emphysema

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Clin Sc 13 6 3-631 November 1954

The results on normal subjects suggest that the factor limiting respiratory effort is the force exerted on the lungs i e each subject appears to have a threshold in terms of force exerted at which he feels dyspneic and this threshold is not affected by inspiratory resistance

At the limit of their respiratory effort patients with emphysema or mitral stenosis may be exerting as great a force on the lungs as normal subjects although the minute volume respired is greatly reduced The range of pressure swing is wide for each group but is similar for all groups apparently because the level of respiratory effort a person will tolerate is affected by the degree of respiratory discomfort he is willing to endure

Increased resistance to respiration in mitral stenosis is the result of increased lung rigidity and in emphysema the result of increased viscous resistance Thus the respiratory minute volume is smaller than although the force exerted on the lungs may be as great as in normal subjects In most patients with mitral stenosis the increase in minute volume for a given increase in oxygen consumption on exercise was greater than in normal subjects partly due to a higher respiratory rate and the effect of the dead space The maximal rate of physical work of which the person is capable depends on the minute volume required at this rate of work and also on the resistance of the lungs to expansion A patient with mitral stenosis or emphysema who reaches his limit of respiratory effort when breathing 30 40 L /minute may be exerting the same force on the lungs as a normal person who reaches his limit when breathing 100 120 L /minute

Oxygen Cost of Breathing The threshold of dyspnea is usually attained when the ventilatory minute volume reaches a certain fraction of the maximal voluntary minute volume (maximal breathing capacity) Thus shortness of breath becomes a function of breathing reserve The work performed by the respiratory muscles to provide a given ventilatory volume may presumably vary considerably due to pathologic changes in the lungs Definition of this important dimension has been so far lacking in establishing a relation between dyspnea and the mechanical performance of the chest bellows

Andre Cournand Dickinson W Richards Jr Richard A

Bader Mortimer E Bader and Alfred P Fishman[3] (Columbia Univ) measured the progressive increments in oxygen requirements of the respiratory muscles as ventilation was stepped up voluntarily by various amounts over and above its *resting level* The subjects voluntarily increased the depth of each breath at a respiratory rate of either 20 or 30/minute then maintained the ventilation thus obtained at a steady level for 25 minutes During the latter part of this period multiple samples of expired air were collected Carbon dioxide was added to the inspired mixture in concentration sufficient to prevent carbon dioxide *unloading from or retention in* the lungs and tissues

A normal man aged 30 with body surface area (B S A) of 2 10 sq m and maximal breathing capacity of 200 L /minute had larger oxygen uptake at a respiratory rate of 20 than at 30 For an excess ventilation of 25 L over and above the resting ventilation each liter of ventilation cost 1 ml oxygen/minute for an excess ventilation of 50 L each liter cost 2 ml /minute and for an excess ventilation of 80 L each liter cost 3 2 ml /minute At this rate if the parabolic curves obtained were extended to 150 L /minute nearly 1 L /minute would be required for ventilation alone

A man 22 with pulmonary granulomas and B S A of 1 67 sq /m and maximal breathing capacity of 120 L /minute had much larger oxygen uptake than the normal subject It was greater at a respiratory rate of 20 than at 30 For an excess ventilation of 50 L over and above resting ventilation each liter cost 3 ml oxygen/minute about one third more than in the normal subject In a man 55 with *chronic pulmonary emphysema* and B S A of 1 52 sq m and maximal breathing capacity of only 30 L /minute for an excess of 5 L of ventilation/minute over and above the resting ventilation each liter cost nearly 25 ml oxygen/minute However with partial relief of the bronchial obstruction *for an excess of 15 L of ventilation* each liter required about 6 ml /minute These data suggest that the increment of work with increased ventilation of 5 L is equivalent to that observed during an increase of more than 50 L in a normal subject In a man 48 with very severe

(3) Tr A. Am. Phys cia • 67 162 173 1954

mitral valve disease and B S A of 1 93 sq m and maximal breathing capacity of 80 L /minute for an excess of 15 L of ventilation over and above the resting level each liter cost 3 2 ml oxygen/minute In a man 32 with much less severe mitral valve disease, at both 20 and 30 respirations/minute the oxygen cost was about the same as in the normal subject

Analysis of Respiratory Response to Carbon Dioxide Inhalation in Varying Clinical States of Hypercapnia Anoxia and Acid Base Derangement James K Alexander

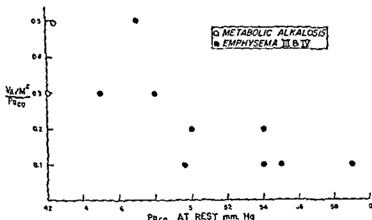


Fig 21—Se t vity t CO t mul s f t on f d g e f CO_2 r t t on O di t e t ty n te m f a d effe t l l r v t l t (l t r s/sq m body f a) a oc ted w th 1 mm Hg r n art rial CO_2 t n Ab art r al CO t n t t (Court y of Alexand r J K t l J Cl I ve t. 34 511 53 Ap 1 1955)

John R West John A Wood and Dickinson W Richards[4] (Columbia Univ) studied 12 normal subjects 13 patients with chronic pulmonary emphysema 3 with cyanotic congenital heart disease 3 with chronic renal disease and uremia and 2 with Cushing s syndrome and chronic metabolic alkalosis To determine sensitivity to carbon dioxide hydrogen ion stimulus three sets of observations were made on each subject The subject breathed in succession room air 3% CO_2 in air and 5% CO_2 in air through a two way low resistance respiratory valve with a dead space of

(4) J Clin I t 34 511 53 Ap 1 1955

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(3) Tr A. Am. Phys 1ns 67 162 173 1954

sitivity in patients with cor pulmonale did not depend on presence of congestive difficulty since other patients without congestive difficulty but with emphysema and CO_2 retention were found to have a reduced sensitivity. Sensitivity was not reduced in three patients with chronic anoxemia secondary to cyanotic congenital heart disease or in three with chronic metabolic acidosis associated with renal failure. Two patients with chronic metabolic alkalosis and CO_2 retention had diminished sensitivity. It was concluded that chronic hypercapnia per se results in diminished sensitivity to the CO_2 inhalation stimulus which is associated with a rise in both arterial CO_2 tension and hydrogen ion concentration.

The authors attempted to correlate the degree of sensitivity change with the amount of CO_2 retention in patients having a reduced response to the carbon dioxide hydrogen ion stimulus. In Figures 21 and 22 sensitivity is expressed both as the change in effective alveolar ventilation per square meter body surface area associated with 1 mm Hg increase in arterial CO_2 tension and as the change associated with unit increase in arterial hydrogen ion concentration. Sensitivity is plotted against the level of arterial CO_2 tension at rest. It is apparent that sensitivity tends to diminish as the resting arterial CO_2 tension increases. No correlation between sensitivity and arterial serum CO_2 content in these same patients is demonstrable.

[This extensive study of the possible mechanism concerned in the decreased sensitivity to the CO_2 inhalation stimulus which occurs in chronic pulmonary emphysema appears to establish that it is the elevated arterial CO_2 tension itself that is responsible. The authors are themselves uncertain of the sequence of events in chronic emphysema which leads to the CO_2 retention but point out that once established it favors increased retention of bicarbonate by the kidney as shown experimentally by Pitts and others thus initiating a vicious cycle of increasing CO_2 retention and diminishing respiratory sensitivity.—Ed.]

EMPHYSEMA BRONCHITIS ASTHMA

Three reports on diamox® (2 acetylamino 1 3 4 thiadiazole 5 sulfonamide) in the treatment of emphysema follow. It is evident from these that despite some favorable effects and apparently low toxicity the place of diamox® as a useful drug for long term administration in emphysema is not established. Dr Heiskell and his co workers demonstrated a consistent reduction in CO_2 combining power to which they attribute the symptomatic benefit which they observed. Dr Lyons and his co workers

60 ml Expired air was collected and arterial blood obtained only after 20 minutes of inhalation

Six patients with chronic pulmonary emphysema and cor pulmonale had markedly reduced sensitivity to the carbon dioxide hydrogen ion stimulus as compared with normal values This reduction might be ascribed to one or more of the following mechanisms (1) increased buffering capacity of the blood associated with elevated plasma bicarbonate level or polycythemia (2) failure of the chest bellows to

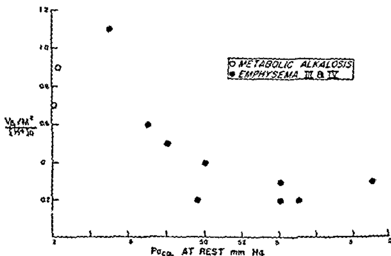


Fig 2—S n t ty t hyd g n n t mulu as f n t on f d g f CO t t on O d t sen t ty n t ms f n re sed ffect l eolar v t l t n (lt s rs/ q m body u f rea) oc t d w h un t r sc n te l pH (bl ths f m l /L) Abse rt l CO ten on t (Cou t y f Al xander K et al J Cl n Inv t 34 511 532 Apr l 1955)

respond adequately to the normal nervous stimuli (3) presence of congestive heart failure chronic anoxemia chronic acidosis or chronic hypercapnia per se The diminished response to CO in the patients with cor pulmonale could not be accounted for on the basis of increased blood buffering capacity since the sensitivity was reduced relative to the hydrogen ion as well as to the CO stimulus Four patients without CO retention but having chronic pulmonary emphysema and a mechanical ventilatory defect similar to that of the cor pulmonale group had normal sensitivity to the carbon dioxide hydrogen ion stimulus The diminished sen

of the urine pH from acid to alkaline range and an increased excretion of bicarbonate was assumed

The venous plasma carbon dioxide combining power was decreased about 6 mEq /L during therapy and this coincided with a remarkably increased exercise tolerance decreased dyspnea and statistically significant improvement in pulmonary function

Effect of diamox® on acid base balance appeared to be imposition of a moderate metabolic acidosis on a pre existing respiratory acidosis Although it has been suggested that this may cause an undesirable depression of the blood pH no adverse effects were noted in the patients studied

Diamox® produced no significant side effects except for muscular cramps in one patient Because of its relative safety and effectiveness when taken orally it appeared to be particularly suitable for treatment of ambulatory patients with chronic emphysema of the lungs

Effects of Carbonic Anhydrase Inhibitor on Arterial Blood Gases in Chronic Pulmonary Emphysema Preliminary Report Harold A Lyons Mohamed Nazih Zuhdi and David M Kydd[6] (State Univ of New York Brooklyn) state that blood carbon dioxide concentration is elevated in some patients with pulmonary emphysema They studied the effect of a carbonic anhydrase inhibitor on such hypercapnia in nine patients with clinical functional and x ray evidence of this disease

Administration of 250 mg diamox® twice daily produced an effect on arterial CO_2 content and Pco_2 at different intervals of time The CO content dropped promptly in every instance irrespective of the initial level and then remained low However arterial Pco behaved differently In six of nine patients Pco fell to significantly lower levels in some instances later than the CO content In three patients there was no significant drop and in one patient an actual increase

Although the pH of four patients decreased initially usually it remained rather constant throughout the period of administration No effect even with clinical subjective improvement was noted on pulmonary hemodynamics cardiac output or pulmonary ventilatory and respiratory

(6) Am J M S 229 193 198 F bru ry 1955

studied the blood gases and found that reduction in CO_2 content was not always accompanied by reduction in Pco_2 and noted in one patient an actual increase Symptomatic benefit appeared to be related to a reduction in Pco_2 when this occurred. They noted no correlation between Pco_2 and Po_2 and found no effect on ventilation measurements even when breathing was subjectively improved Dr Bell and his associates found decreased Pco_2 and increased Po_2 whenever plasma bicarbonate and pH were decreased and they relate these changes which were observed after three days administration at the level of 10 mg/kg/day to improved alveolar ventilation as the result either of hyperventilation or of fluid loss Symptomatic improvement however was not long sustained in their patients all of whom had severe emphysema with respiratory acidosis and it did not occur in all instances These workers noted that within four hours after a large oral dose of diamox® there was increased alveolar ventilation as indicated by increased Po_2 although the Pco_2 actually increased in this interval This they consider evidence for inhibition of carbonic anhydrase activity in the *red cell* Such action they believe opposes the other effects of diamox® (i e water diuresis and metabolic acidosis produced by its action in the kidney) and the effect on Pco_2 is the resultant of the magnitude of these opposing actions dependent on the dose Dose time factors therefore may explain some of the conflicting reports concerning the chemical effects of this drug

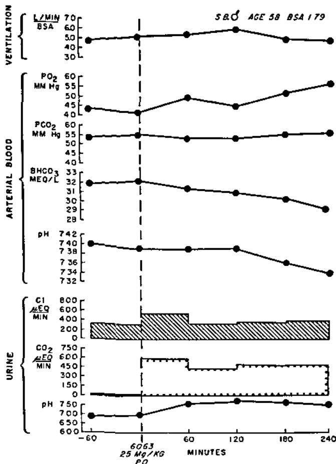
These reports concern the effects of diamox® only in emphysema without severe congestive heart failure due to cor pulmonale Its use as a diuretic in such patients has been reported by W B Schwartz *et al* (Ann Int Med 42 79 1955) —Ed

Treatment of Chronic Emphysema of Lungs with Diamox® (Carbonic Anhydrase Inhibitor) is discussed by Charles L Heiskell Jr Jay B Belsky and Benjamin F Klaumann[5] (V A Hosp Long Beach Calif) Diamox® produces an increased urinary excretion of sodium potassium bicarbonate and water and a decreased excretion of ammonia This is accomplished by inhibition of carbonic anhydrase in the renal tubular cells The drug was tried on patients with chronic emphysema

METHOD —Four emphysematous and one control patient were given a diet containing 0 9 Gm sodium and 2 6 3 5 Gm. potassium a day Each patient was allowed to drink water at will and fluid intake and output were charted Urinary and blood electrolytes pH and blood CO_2 were measured daily Diamox® was administered at eight hour intervals in a total daily dosage of 10 mg/kg for four days Each patient estimated his dyspnea for the preceding 24 hours Patients were encouraged to walk about and to keep records of their physical activities

Studies of urinary electrolyte excretion showed that even with a diet containing less than 1 Gm sodium/day diamox® led to a significantly increased excretion of sodium and potassium a decreased excretion of ammonia and no significant change in chloride excretion There was a shift

(5) J A M A 156 1059 1063 No 11 1954



F g 3—A t ff t f or l dm t ton f d m ® (25 mg/kg) u
rt l bl d d l tion (C rt y f B ll A L L t l Am J M d 18 536-
546 Ap l 1955)

measurements Alterations in the electrolytes of the serum after administration of diamox® were variable

Although symptoms of CO retention have generally been ascribed to acidosis rather than to Pco in this series clearing of the mind and improvement in general well being were noted in emphysematous patients in whom a significant decrease in arterial Pco followed administration of diamox® However clinical improvement did not always appear

The mechanism of action is obscure The storage reservoir of CO_2 should be increased greatly in pulmonary emphysema Diamox® by its action on carbonic anhydrase may be able to mobilize these stores promoting a loss from the body and thus over a prolonged period actually causing a decrease in arterial Pco_2 without requiring other mechanisms

Effects of Carbonic Anhydrase Inhibitor 6063 (Diamox®) on Respiration and Electrolyte Metabolism of Patients with Respiratory Acidosis A L Loomis Bell Jr Craig N Smith and Eric Andreae[7] (New York) studied seven patients with proved pulmonary emphysema and chronic CO retention Acute effects of oral administration of large doses of diamox® (25 mg/kg) in a typical patient are plotted in Figure 23 Figure 24 shows the effects of continued oral administration of large doses

In most instances diamox® induced copious diuresis of alkaline urine containing large quantities of sodium potassium and bicarbonate On continued administration the excretion pattern reverted to control values within a few days but metabolic acidoses (plasma bicarbonate and pH decreased below control values) and the dry weight of the patient persisted

Diamox® improved alveolar ventilation as measured by increased PO and decreased Pco after three days of continued dosage Alveolar ventilation increased without consistent increase in minute ventilation but was always associated with significant diuresis Increased alveolar ventilation was noted within four hours after a large oral dose of diamox® although the Pco of arterial blood increased during this interval which is considered evidence of inhibi

(7) Am J Med 18 536-546 Ap 1 1955

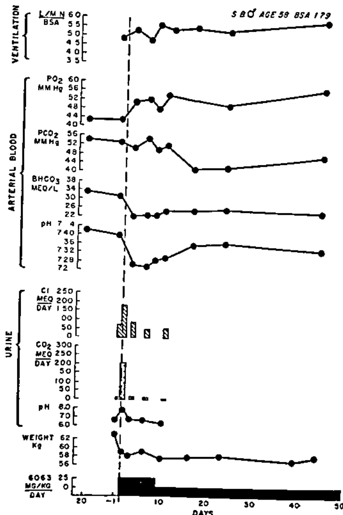
Physiologic Evaluation of Effects of Diaphragmatic Breathing Training in Patients with Chronic Pulmonary Emphysema was made by William F Miller[8] on 24 patients who had achieved optimal benefit from conventional treatment They were studied before and six to eight weeks after training in diaphragmatic breathing

Diaphragmatic breathing training increases diaphragmatic excursion providing a more effective tidal volume at slower respiratory rate with no significant change in total ventilation When total ventilation is diminished before treatment an increase usually results after diaphragmatic training The increased inspiratory capacity suggests a lowering of the respiratory midposition and decrease in functional residual capacity The result is more effective alveolar ventilation as shown by increased arterial O % saturation and decreased Pco The increased three second vital capacity and maximal breathing capacity indicate improved velocity air flow important in increased exercise tolerance Objective evidence of increased exercise tolerance is shown by decreased postexercise dyspnea time and increased postexercise O_2% saturation Diaphragmatic breathing training also increases efficiency of the cough mechanism with improved evacuation of bronchial secretions thus leading to better control of bronchial infections

Action of Breathing Exercises in Pulmonary Emphysema E J M Campbell and John Friend[9] (Middlesex Hosp London) studied ventilatory function in 12 emphysematous men before and after a course of instruction in breathing exercises Electromyographic recordings were made of the sternocleidomastoid rectus abdominis and external oblique muscles of seven patients after quiet breathing after mild exercise during voluntary maximal expiratory efforts and while rebreathing expired air after carbon dioxide was removed In all patients total lung capacity and its subdivisions maximal breathing capacity and effective tidal volume were determined

Breathing exercises were taught to the patients individually two or three times weekly for four to six weeks The theoretical aims were to (1) relax accessory muscles of res

(8) Am J M d 17 471 477 O t be 1954
(9) La t 1 3 5 329 F b 13 1955



F g 24 —Effect of o t d dm tr t on f la ge d f d m ® in resp r t y d (Cou t y f Bell \ L L *et l* Am J M d. 18 536 546 Ap l, 1955)

tion of carbonic anhydrase activity of the red cell Most patients receiving the drug exhibited some symptomatic improvement for about two weeks followed by return of pretreatment symptoms In two severely ill patients diamox® failed to produce significant improvement

The sputa of seven of eight patients yielding pneumococci before treatment failed to yield them after a course of penicillin intramuscularly Hemophilus influenzae if present before treatment were recovered from sputum after penicillin therapy Chloramphenicol reduced the number of H influenzae in the sputum but failed to eliminate them entirely Pneumococci were present in the sputum after chloramphenicol therapy in two instances and after oxytetracycline in one

Air Pollution and Bronchitis is discussed by John Pemberton and C Goldberg (Univ of Sheffield) The crude death rate from bronchitis shows a steady and marked increase in passing from rural areas to the towns cities and conurbations Attention has recently been directed to air pollution as a possible cause and the great increase in deaths mostly from bronchitis during and immediately after a prolonged smoke fog in London in 1952 has added weight to this hypothesis

The extent to which bronchitis death rates vary with the average air pollution from sulfur dioxide and solid matter was estimated for the county boroughs of England and Wales Sulfur dioxide has fallen under suspicion because it has been shown to exert an effect on human respiratory function in concentrations met with in smoke fogs Amdur *et al* found that inhalation in concentrations of 1 8 parts per million increased the pulse and respiratory rates in normal human volunteers and caused the respiration to become more shallow

A significant correlation was found between average sulfur dioxide air pollution and mortality rates for bronchitis in men aged 45 and over for the years 1950 1951 and 1952 In only two of six sets of data was there a similar association for women of the same age The association between air pollution with solid matter and mortality rates was much less consistent Only three of the six sets of data on men and two on women were significant

There was no significant correlation between average sulfur dioxide pollution and two indexes of general social conditions based on income and housing conditions The

(2) B t M J 2 567 570 Sept 4 1954

piration (2) increase diaphragmatic movement by active lowering of the costal margins by contraction of the lateral abdominal muscles (3) obtain the use of lung bases by localized lateral basal expansion and (4) make expiration the active phase of respiration

The changes found were those of slow deep breathing Inspiration is mechanically inefficient in ventilating the lung in emphysema where the chest is raised and expanded and the diaphragms are flattened and depressed If however the chest is deflated by a preliminary expiration the inspiratory muscles can act more efficiently

The only evidence of benefit from the exercises was that several patients appeared to be relieved of dyspnea due to physical exercise more rapidly by exercise breathing than by natural breathing

Chronic Bronchitis and Emphysema Significance of Bacterial Flora in Sputum Curtland C Brown Jr Marion B Coleman Ralph D Alley Allan Stranahan and C H Stuart Harris[1] (Albany N Y) report a study of the source of pathogenic bacteria in sputum of patients with chronic bronchitis and emphysema and of the effect of penicillin or broad spectrum antibiotic therapy on quantity and bacterial flora of the sputum

METHOD —After at least three days of sputum collection bronchoscopy was performed and bronchial secretion aspirated into a mixture of 50% broth in saline Swabs from the posterior nasopharynx and pharynx were taken from many patients Sputums swabs and the centrifuged deposits from the bronchial specimens were cultivated on blood agar aerobically and anaerobically Colonies were picked after 24 hours incubation and identified by microscopic cultural and biochemical study

In some patients the flora of the bronchoscopy specimen and of the sputum was the same but in 8 of 16 patients with pneumococci or Hemophilus influenzae in the sputum no similar organisms were found by bronchoscopy This variation could be due either to clinical differences or to unsatisfactory specimens Also single bronchoscopic specimens may not represent secretions from all areas as do sputa collected over a prolonged period The nasopharyngeal swabs did not yield pathogenic bacteria so frequently as the sputum

(1) Am J M d. 17 478 484 O tober 1954

chloride and use of antibiotic drugs in the presence of bronchial and sinus infections

[More recent studies by the same workers indicate that meticorten® (prednisone) or meticortelone® (prednisolone) at dosages one third to one fourth those of hydrocortisone are more satisfactory in the management of these conditions than the older corticosteroids (Barach A L Report Presented at the First International Conference on the Clinical and Metabolic Effects of Meticorten and Meticortelone May 31 June 1 1955) —Ed]

Effects of 9α Fluorohydrocortisone Acetate Administered to Patients with Asthmatic Bronchitis Coolidge S Wakai and Louis E Prickman[4] treated four patients for 8 17 days administering 6-16 mg fluorohydrocortisone daily in divided doses Edema was noted in three patients with weight gains of 3½ 7½ lb The serum potassium value dropped in one patient while the serum sodium level remained within normal range The effect on asthma was variable One patient had no symptomatic relief one had subjective improvement the third probably improved because of other measures and the fourth responded satisfactorily

Clinical experience apparently indicates that fluorohydrocortisone is not a superior preparation for suppression of bronchial asthma and that an unduly high incidence of edema is associated with its use No therapeutic advantage over ACTH or cortisone was found in the present study The potent action of fluorohydrocortisone resulting in development of considerable edema within a few days is a significant disadvantage adding another problem to treatment of patient with asthma

CONGENITAL DISORDERS

Congenital Lobar Emphysema R H White Jones and L J Temple[5] state that the symptoms of congenital lobar emphysema are fairly characteristic and consist in increasing attacks of dyspnea and cyanosis A history of such attacks calls for a roentgenogram of the chest which should be repeated a few days later if there is nothing apparent on the first film The increasing emphysema of the affected lobe will gradually become more obvious clinically and

(4) P oc St ff M t M y Cl 29 663 66 Dec 22 1954
(5) A h D s Ch ldh od 29 248 253 July 1954

evidence supports the hypothesis that sulfur dioxide air pollution is a factor in the bronchitis death rate of middle aged and elderly men

Comparative Results of Use of ACTH Cortisone and Hydrocortisone in Treatment of Intractable Bronchial Asthma and Pulmonary Emphysema Hylan A Bickerman and Alvan L Barach[3] (New York) gave 163 patients with intractable asthma and pulmonary emphysema with bronchospasm 309 courses of ACTH cortisone or hydrocortisone ACTH and cortisone led to complete or partial remission in 82 3 and 86 2% of the courses respectively Hydrocortisone administered at a dosage level averaging 50 60% of that of cortisone achieved the same effect in 96% of the courses

Duration of remission induced by the short intensive courses of either ACTH cortisone or hydrocortisone was two to three weeks Patients with bronchial asthma generally manifested a more complete remission than those with the bronchospastic type of pulmonary emphysema

Hydrocortisone effects differed from those of cortisone in (1) swifter onset of therapeutic benefit i e in 18 36 hours with hydrocortisone as compared to 4 5 days with cortisone (2) decreased dosage requirement of approximately one half to two thirds of the cortisone dosage for comparable effect and (3) significant reduction in side reactions

Best results were seen with (1) patients in whom persistent bronchospasm was the result of exposure to seasonal factors such as pollen and (2) patients in whom the asthmatic state had been previously moderately well controlled but in whom intractable bronchospasm followed an upper respiratory infection Although short intensive courses of ACTH or the steroids seemed preferable to maintenance therapy in these two groups in 21 of the 30 patients with chronic intractable asthma pulmonary fibrosis and advanced pulmonary emphysema clinical improvement was maintained for 9 24 months by 20-75 mg cortisone or hydrocortisone/day

Side effects of the corticosteroids and ACTH were lessened by a low sodium diet administration of potassium

(3) J All gy 25 312 324 J ly 1954

sociated with chondromalacia mucosal folds venous anomalies pressure of a patent ductus arteriosus and pressure of a congenital diaphragmatic hernia A defect in the anterior mediastinum associated with herniation of a lobe and kinking of its bronchu can cause the condition The possibility has been noted that intratracheal insufflation with too high an oxygen pressure in the resuscitation of asphyxia neonatorum may be a contributory or principal cause of lobar emphysema in infancy —Ed]

Vascular Anomalies Associated with Interpulmonary Bronchial Cysts are reported by Wil on Weisel John W Docksey and Marvin Glicklich[6] (Marquette Univ)

CASE 1 —Man 25 was hospitalized with productive cough right

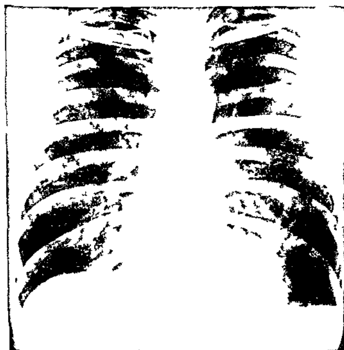


Fig 25 —P t t th h w g f e d d ty l ft l h t th ght t p t ba l t l t (C t y f W) W t l Am R T b 71 573 583 Ap l 1955)

chest pain fever and chills for two weeks and history of probable pneumonia a year before X ray studies and bronchoscopy led to diagnosis of lung abscess Thoracotomy revealed a firm round lesion in the posterior and medial basilar segments of the right lower lobe

(6) Am Rev T b 71 573 583 Ap 1 1955

roentgenologically The authors report a case of congenital lobar emphysema associated with a diaphragmatic abnormality in a newborn baby

Baby boy had a cyanotic attack two days after normal delivery Examination showed diminished air entry over the right lung suggesting atelectasis He improved after administration of oxygen Four days later cyanotic attacks recurred and dyspnea and cyanosis became more constant Roentgenograms of the chest showed collapse of the right upper lobe with slight mediastinal displacement to the right During the next few days symptoms became more pronounced Further x ray examination revealed marked herniation of left upper lobe across the midline leading to compression of right upper lobe A provisional diagnosis of congenital cyst of the lung was made and surgical intervention undertaken

The left upper lobe was voluminous and had the appearance of a pink souffle There were no adhesions although there was a small area of congenital fusion to the lower lobe which was fetal in appearance The change in the upper lobe appeared to affect the whole lobe and no normal lung tissue was noted in it The upper lobe bronchus was clamped and upper lobectomy was carried out The chest was closed with drainage Postoperatively it was no longer necessary to administer oxygen and successive films showed expansion of the left lower lobe

The pathologist described an aerated upper lobe showing some emphysematous blebs under the pleura On section it contained several emphysematous cysts the largest of them being about 1 cm across and there was moderate diffuse emphysema Areas of intensified emphysema were present which appeared to communicate with the hilar connective tissue No bronchial abnormality was seen Microscopically there were no inflammatory changes

A roentgenogram four months after operation showed a satisfactory state of affairs but several translucent areas at the right base suggested herniation of the bowel through the diaphragm A barium meal a year after the operation confirmed the fact that a fairly large part of the ileum and the midtransverse colon had herniated through the diaphragm and was lying in the anterior mediastinum There was no x ray evidence of this hernia before surgery

A curious feature of congenital lobar emphysema is that only the upper lobes or right middle lobe are involved No cases affecting the lower lobes have been reported Differential diagnosis lies between atelectasis interstitial emphysema agenesis congenital cyst lobar emphysema secondary to the viscid secretions of bronchitis foreign body and diaphragmatic hernia pressing on the lung

[The reader is referred to the original article for a review of the literature and discussion of the pathogenetic factors in this condition Various causes of bronchial obstruction have been observed or postulated including deficient cartilage rings flaccidity of the bronchus presumably as

A vessel was found which went from the lower posterior basal area to the azygos vein entering below the level of the fifth rib

CASE 4—Man 35 had left chest pain cough and dyspnea for two days Since age 2 he had had seven episodes of pneumonia the most recent 11 years previously Coarse rales were heard at the left base posteriorly X ray (Fig 25) showed posterior basal atelectasis A left thoracotomy revealed that the posterior basilar area was clearly demarcated by its pink color and lack of anthracosis On dissection of the inferior pulmonary ligament and incision of the posterior mediastinal pleura four large vessels were encountered which arose from the aorta and were traced to the posterior basal segment which was distorted by a large firm mass (Fig 26) These vessels were 1 cm to 3 mm in diameter and had the appearance and consistency of large systemic or peripheral arteries Histologic examination revealed a multiloculated cyst with a gray mucosal lining There were no demonstrable bronchial communications with the cyst or communication of abnormal vessels with the pulmonary circulation

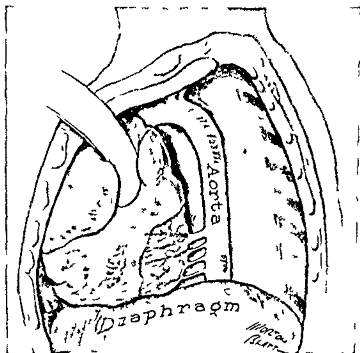
CASE 5—Man 39 had had dull aching right chest pain since a lesion of the lower right lobe had been discovered 11 years before X ray disclosed a rounded density in the medial basilar area and intrapulmonary bronchogenic cyst was diagnosed Thoracotomy revealed a firm mass in the posterior and medial basilar segments which appeared distinct from the rest of the lung because of lack of crepitation a pale nonpigmented color and incomplete fissure A large artery coming from the aorta just above the aortic hiatus entered the lesion containing area on the diaphragmatic surface

Fatalities have been reported as a result of serious technical difficulties arising from injury to the anomalous vessels In this series there was no clearcut clinical syndrome which distinguished the intrapulmonary bronchial cysts from other chronic pulmonary diseases The prominent feature was the chronic and recurring nature of the symptoms X ray findings were those of possible abscess segmental atelectasis suggestive of carcinoma a round lesion and a definite cystic appearing lesion One gross characteristic common to all five cases was absence of anthracotic pigmentation in the cystic area and the pale pink color of the lung When this condition is present anomalous vessels should be sought if resection is planned

Pathologically the pulmonary lesions were characterized by cystic structures usually lined by columnar or ciliated epithelium with cartilage and mucous glands in the wall and varying degrees of inflammation in surrounding parenchyma Grossly and histologically the anomalous arterial branches were typical of peripheral arteries An un

This area was sharply demarcated by its light pink color contracted state and definite fissure separating the involved segment from the rest of the lower lobe A pulsating tortuous vessel ran from the lower thoracic aorta to the posterior segment of the right lower lobe

CASE 2—Man 37 had small hemoptyses for 11 months X ray studies showed a circumscribed mass in the medial basal segment of the right lower lobe Thoracotomy revealed a mass in the posterior basal portion of the lobe which was clearly demarcated from the rest



F g 26—D g m f four malou rt bra he t ri g post r port of left l w l be (Cou t y f W l W t l Am R T berc 71 573 583 Ap l 19 5)

of the lung by its pale pink color and an incomplete fissure Three *abnormal* vessels entered the posterior segment of the lower lobe the most cephalad arose from the seventh right intercostal artery *and the other* two from the aorta

CASE 3—Man 41 had had progressive productive cough hemoptysis weakness and dyspnea for seven years Bronchograms showed cystic spaces and saccular bronchiectasis of the right lower lobe basal segments A right thoracotomy revealed a complete lack of crepitation in the basilar portion of the lobe which was pale pink

had had slight shortness of breath for six months She had only a slight cough On fluoroscopy the left pulmonary artery seemed larger than normal Angiocardiography revealed absence of the right pulmonary artery and a large left pulmonary artery Linear shadows in the right lung which had been erroneously interpreted as old tuberculous infiltrates were demonstrated to be hypertrophied bronchial arteries No specific therapy was recommended

CASE 3—Girl 4 months old was hospitalized for intermittent cyanosis dyspnea and fever After a normal postnatal period she had two episodes of cyanosis preceded by coughing and followed by vomiting which brought relief After transient improvement she died Autopsy revealed confluent lobar pneumonia The heart weighed 80 Gm The coronary arteries arose normally One centimeter above the aortic valve a vessel 2 7 cm in diameter arose from the left side of the aorta and crossed the mediastinum to enter the right lung The pulmonary artery was of normal caliber There was one branch to the left lung but none to the right Microscopic examination of the left and the abnormal right pulmonary artery failed to show any difference in their mural structures

CASE 4—Girl 12 complained of being short of breath on exercise She had no history of pulmonary infection Several years before a bronchogram demonstrated an anomalous right bronchial tree without evidence of bronchiectasis Since she apparently had more normal pulmonary tissue than is present after pneumonectomy and yet had more shortness of breath than one would expect in a 12 year old person after pneumonectomy it was considered probable that the pulmonary disability was due to abnormal blood flow to some of the pulmonary tissue

The right hemithorax was explored Except for a small free pleural space the lung was joined to the chest wall and mediastinum by avascular connective tissue The pulmonary tissue in general appeared normal There was a systemic artery about 6 mm in diameter perforating the dome of the diaphragm slightly posterior to the midline in an anteroposterior plane A second systemic artery was found more posterior and somewhat more medial close to the vertebral bodies It too came through the diaphragm measured about 8 mm in diameter and divided into a small and large branch before entering the lung posteriorly in the paramediastinal portion These two arterial branches were dissected out ligated and divided The postoperative course was uneventful

CASE 5—Woman 36 had dyspnea on exertion for 17 years It was known that the heart was in the right side of the chest Physical examination revealed a thin woman without cyanosis The lung fields were clear The bronchogram did not outline the bronchial tree of the middle or right lower lobe the bronchial tree of the left lung appeared normal Thoracotomy demonstrated no free pleural space The right hemithorax contained a unilobar lung The heart occupied a considerable part of the lower and anterior portion of the right hemithorax As the lung was freed from the diaphragm several ves

usual characteristic was arteriosclerotic changes in most of these arterial divisions

[In recent years there have been numerous reports in the surgical literature of anomalous arteries to the lung from the systemic circulation found in association with pulmonary cysts bronchiectasis and sequestration of a part of the lung This condition is not well known to internists and the diagnosis is infrequently made preoperatively

In the following article Maier discusses the relationship of such anomalous systemic arteries to anomalies of the pulmonary artery itself and presents instances of systemic arteries to the lung in association with (1) absence of a pulmonary artery or (2) hypoplasia of one lung Surgical intervention such as ligation of anomalous vessels or removal of nonfunctioning lung appears in selected instances to be of value in relieving patients of such symptoms as dyspnea from vascular congestion recurrent hemorrhage or recurrent infection —Ed]

Absence or Hypoplasia of Pulmonary Artery with Anomalous Systemic Arteries to Lung Herbert C Maier[7] (Columbia Univ) states that the pulmonary vascular plexus *at one stage of embryologic* development has important dorsal branches from the aorta which normally disappear but may persist when there is faulty development of the pulmonary artery Although most recently reported cases of anomalous systemic arteries to the lungs have been discovered because of the associated presence of bronchogenic cysts bronchiectasis or sequestration of lung tissue anomalous arteries from the aorta or its branches may enter grossly normal pulmonary tissue Anomalies of bronchial branching and lobar development may also be present

The clinical features in cases of absence or hypoplasia of the pulmonary artery to one lung are presented in the following examples

Case 1 —Boy 3 had a history of recurrent pneumonia productive cough and occasional hemoptysis His respiratory symptoms dated to infancy when coughing and wheezing were noted Bronchiectasis had been suspected but several bronchograms had been normal Angiocardiograms revealed absence of the right pulmonary artery At pneumonectomy the visceral pleura of the lung was a thickened layer and had numerous tiny bronchial vessels coursing over its surface There was evidence of bronchial collateral circulation in the region of the pulmonary ligament and over the lower portion of the hilus but this was less marked over the upper lobe where a 4 mm systemic artery entered the lung No vessel at all was found where the pulmonary artery is normally located There was no evidence of anomalous pulmonary venous drainage The right lung was *removed* and the postoperative course was uneventful

Case 2 —Woman 37 had a tight feeling in the right chest and

(7) J Thorac Surg 28 145 16 August 1954

entiated adenocarcinoma a tumor dose of 6 000 r in five to six weeks is given when there is a chance for prolonged control of the disease and a smaller dose if intrathoracic metastases are extensive In oat cell carcinoma with high probability of hepatic and cranial metastases a 3 000 r tumor dose is given in nine days If both lungs are involved the more diseased one is irradiated first with a tumor dose of 2 000 r in eight days if there is a satisfactory response the other lung is similarly treated Tissue doses over 2 500 r cause pneumonitis two to eight weeks after irradiation which may be alleviated by cortisone 200 300 mg /day

In some instances of far advanced bronchogenic carcinoma nitrogen mustard 0 4 mg /kg intravenously in a single dose is used in conjunction with x rays In the superior vena cava syndrome HN produces prompt relief in most patients with objective evidence of tumor regression If response to HN is incomplete and the blood count is not unduly depressed in three weeks another dose of 0 2 or 0 4 mg /kg may be given In pleural involvement x ray therapy intrapleural instillation of radioactive gold (Au^{198}) or HN may control the effusion After removal of the pleural fluid usually 75 100 mc Au^{198} or 20 30 mg HN is instilled Occasionally triethylene melamine (TEM) has been used in widespread lung cancer Although the effects are similar to those of HN the latter is preferred for its prompt and consistent action

Multiple pulmonary metastases of certain radiosensitive cancers may be irradiated even in the absence of symptoms since a tumor dose of 2 000 2 500 r to the whole chest can cause their disappearance without producing more than temporary pneumonitis X ray therapy is sometimes preceded by a course of HN_2 or TEM

Pulmonary metastases from breast cancer occasionally respond to hormonal treatment If there is no improvement or relapse occurs after surgical castration 100 mg testosterone propionate is given intramuscularly three times weekly Adrenalectomy has caused further improvement particularly when the patient has improved after castration and testosterone Cortisone may help patients unresponsive to castration and testosterone In postmenopausal women hormonal treatment has consisted in trials of

sels were found penetrating the diaphragm close to the midline and entering the pulmonary tissue Two of these were systemic arteries and one of them was ligated and divided

CASE 6—Boy 14 had frequent upper respiratory infections a persistent cough which gradually became productive and moderate dyspnea on exertion Roentgenogram showed a shift of the heart and mediastinum to the right elevation of the right diaphragm and intercostal narrowing due to diminished volume of the right lung A bronchogram showed the right main stem bronchus ending in a blind sac

At operation the right pleural cavity was obliterated by dense and vascular adhesions There were several firm bands from the diaphragmatic pleura to the lower surface of the lung containing vessels 2 3 mm in diameter There were no normal pulmonary arteries or veins on this side A large vein left the single lobe ran parallel to the bronchus and emptied into the superior vena cava The hypoplastic right lung was removed

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NEOPLASMS

Treatment of Inoperable Pulmonary Cancer Primary and Metastatic David A Karnofsky W P Laird Myers and Ralph Phillips[8] (Memorial Cancer Center New York) state that of the estimated 20 000 new cases of primary bronchogenic carcinoma diagnosed each year in the United States probably less than 5% are satisfactorily controlled by surgery In about one third of patients with metastatic lung lesions respiratory symptoms constitute the major problem The most effective treatment is interference with growth and extension of the neoplastic cells accomplished with ionizing radiation or specific drugs

If at thoracotomy the primary bronchogenic tumor or metastatic lymph nodes are not resectable they should be implanted with radon seeds which deliver a tumor dose of 8 000 12 000 r with minimum risk of damage to surrounding structures In inoperable cases without evidence of distant metastases irradiation is advisable even in the absence of disabling symptoms In the presence of symptoms with or without distant metastases x ray therapy produces symptomatic relief in about 70% of patients

Bronchogenic cancer is best irradiated with supervoltage x-rays or with hard gamma rays For epidermoid and differ

(8) Am J Surg 89 526 537 February 1955

entiated adenocarcinoma a tumor dose of 6000 r in five to six weeks is given when there is a chance for prolonged control of the disease and a smaller dose if intrathoracic metastases are extensive In oat cell carcinoma with high probability of hepatic and cranial metastases a 3000 r tumor dose is given in nine days If both lungs are involved the more diseased one is irradiated first with a tumor dose of 2000 r in eight days if there is a satisfactory response the other lung is similarly treated Tissue doses over 2 500 r cause pneumonitis two to eight weeks after irradiation which may be alleviated by cortisone 200 300 mg /day

In some instances of far advanced bronchogenic carcinoma nitrogen mustard 0 4 mg /kg intravenously in a single dose is used in conjunction with x rays In the superior vena cava syndrome HN produces prompt relief in most patients with objective evidence of tumor regression If response to HN is incomplete and the blood count is not unduly depressed in three weeks another dose of 0 2 or 0 4 mg /kg may be given In pleural involvement x ray therapy intrapleural instillation of radioactive gold (Au^{198}) or HN_2 may control the effusion After removal of the pleural fluid usually 75 100 mc Au^{198} or 20 30 mg HN is instilled Occasionally triethylene melamine (TEM) has been used in widespread lung cancer Although the effects are similar to those of HN the latter is preferred for its prompt and consistent action

Multiple pulmonary metastases of certain radiosensitive cancers may be irradiated even in the absence of symptoms since a tumor dose of 2 000 2 500 r to the whole chest can cause their disappearance without producing more than temporary pneumonitis X ray therapy is sometimes preceded by a course of HN_2 or TEM

Pulmonary metastases from breast cancer occasionally respond to hormonal treatment If there is no improvement or relapse occurs after surgical castration 100 mg testosterone propionate is given intramuscularly three times weekly Adrenalectomy has caused further improvement particularly when the patient has improved after castration and testosterone Cortisone may help patients unresponsive to castration and testosterone In postmenopausal, hormonal treatment has consisted in trials of

estrogens androgens castration combined adrenalectomy and castration and cortisone in far advanced cases

In pulmonary or osseous metastases from carcinoma of the prostate a combination of estrogens and castration is frequently used *Pulmonary lesions of thyroid cancer* respond to x ray therapy and if capable of concentrating iodine to radioactive iodine

Early and apparently localized Hodgkin s disease of the mediastinum is usually treated with a tumor dose of 2,400 3 000 r in three to five weeks In some cases of mediastinal and cervical or axillary disease the authors have given HN followed by x rays to the tumor bearing area For recurrent mediastinal involvement or parenchymal disease x ray doses should be adequate to cause tumor regression In some instances HN or TEM may be effective The varieties of lymphosarcoma are usually managed in the same manner as Hodgkin s disease although they do not respond as consistently to treatment

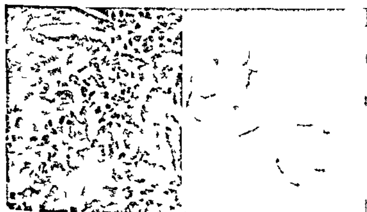
Acute leukemia may respond to adrenal cortical steroids folic acid antagonists (aminopterin and amethopterin) and 6 mercaptopurine The most consistent and favorable results have been obtained in children The histologic picture of pulmonary metastases in children is not a reliable guide to radiosensitivity and the temporary response to x rays is sometimes good

While specific therapy offers the only chance of relieving the underlying disease many major problems require supportive measures

Pulmonary Adenomatosis is discussed by Seymour M Farber David A Wood Franco Sangalli Samuel L Pharr and Rukmono[9] (Univ of California) Storey Knudtson and Lawrence analyzing 205 cases stated that in pulmonary adenomatosis the alveoli are lined by columnar or cuboidal epithelial cells with eosinophilic cytoplasm and basally placed nuclei and stressed the typical preservation of the pulmonary architecture in this condition They as well as other investigators concluded that these lesions are carcinomas of bronchiolar origin Many of them probably have been misdiagnosed as bronchogenic carcinoma Men and women of cancer age are equally affected

(9) S g Gy ec & Ob t 99 483 491 O t ber 1954

The commonest symptom is cough producing large amounts of mucoid foamy sputum Dyspnea chest pain physical signs and laboratory findings are not specific The condition is usually recognized only at surgery or at post mortem examination Roentgen signs are variable and atypical Lesions range from a solitary unilateral nodule (in one fourth of the reported cases) to multiple bilateral nodules of varying size and shape The nodules often coalesce to form homogeneous densities Numerous investi



Fg 27 (l ft) —Typ l l g ect on p lmon y d m t h w g b dant ll la m t ll g w th l l r pa 09
Fg 28 (ght) —C ll n n sp t m N t e t vac lat on d t gh f g oup g ×471
(C rt y f Fa ber S M *t al* S g Gy ec & Ob t 99 483 491 O t b 1954)

gators have stressed the abundance of diagnostic cells in the sputum In lung sections these cells are seen within alveolar spaces (Fig 27) This exfoliation of the growth seems to be more profuse in adenomatosis than in typical carcinoma of the lung

The problems involved are well illustrated in the following case

Woman 70 had a cold associated with cough productive of increasing amounts of sputum Physical examination revealed disease in the left upper lung field Laboratory studies were noncontributory except for malignant cells in the sputum (Fig 28) Patient died five months after onset of symptoms At autopsy the lateral surface of the left upper lobe was scarred and dark red and contained a firm

grayish tumor Alveolar walls were lined by tall columnar and cuboidal cells Metastatic tumor cells were also found in one hilar lymph node

The sputum was studied in three more cases Grouping of cells in all instances was consistent with malignancy resembling the acini of adenocarcinoma However appear ance of the nuclei which was not typical of cancer cells was evidence against a group V diagnosis of malignancy

Although cytologic study of the sputum does not detect pulmonary adenomatosis with unfailing accuracy it fre quently suggests its presence

[The inclusion of this disorder among the pulmonary neoplasms follows the usual current practice and belief that despite its resemblance to the communicable disease jaagsiekte of animals the disease in man is a form of cancer It is believed not to be transmitted from animals to man nor to be communicable among human beings The authors nevertheless prefer to retain the designation pulmonary adenomatosis" because it avoids the etiologic bias of such alternative designations as alveolar cell carcinoma bronchiolar carcinoma multicellular papillary adenocarci noma etc Of these alternative designations the one most probably to be preferred is bronchiolar carcinoma since the preponderance of evidence favors this conception of its histogenesis —Ed]

Calcification within Carcinoma of Lung Report of Case with Isolated Pulmonary Nodule Seymour B London and William J Winter[1] (V A Hosp Coral Gables Fla) state that 15 30% of the surgical specimens of isolated pulmonary nodules have been found to be primary malignant lung tumors 50% granulomas and the remainder benign tumors metastatic lesions lung cysts and miscellaneous lesions At tempts to differentiate the benign from the malignant le sion by x ray and laboratory technics have been held to be unreliable except for the x ray finding of calcification with in the nodule It is generally accepted that the presence of calcium in a pulmonary shadow is suggestive of a benign lesion and most intrapulmonary nodules containing calcium need not be removed

The authors report a case of a malignant isolated pul monary nodule containing calcium within its substance

Man 55 was hospitalized after discovery of a solitary pulmonary lesion There had been no hemoptysis chest pain or wheeze He had been hospitalized for pulmonary tuberculosis 30 years before X rays revealed a rounded sharply circumscribed nodular density in the left midlung field 2 5 cm in diameter an increase of 0 5 cm over its size 18 months previously Spot film and tomographic tech

(1) A M A Ar h I t M d 94 161 165 J ly 1954

death rate and if so what diseases are involved There were 394 counties selected as study areas on the basis of population and availability of volunteers to carry out field work The areas varied from very large cities to small towns and farming districts

Over 22 000 volunteers recruited and trained for the study were organized in groups of 5 15 persons with a chairman responsible for the work of each group Each researcher asked 5 10 white men aged 50-69 to fill out smoking questionnaires Names and addresses of all the men questioned were entered on a follow up report form four copies of which were prepared immediately The follow up form also carried the name and address of the researcher and a substitute The completed smoking questionnaires were then forwarded to the authors and the follow up forms retained in the field for future use Questioning began in January 1952 and was largely completed by the end of May The first follow up was started in November 1952 Each researcher was given a follow up form with the names of the men to whom she had previously given a questionnaire For each man on her list she was asked to check alive dead or don t know

It was found that men with a history of regular cigaret smoking have a considerably higher death rate than men who have never smoked or men who have smoked only cigars or pipes A total of 3 002 deaths occurred among men with a history of regular cigaret smoking If they had died at the same rate as men who never smoked there would have been only 1 980 deaths Death rates increase with amount of cigaret smoking A total of 745 deaths occurred among men who were smoking a pack or more of cigarets a day at the time they were questioned Only 426 of them would have died if their death rates had been the same as for men who never smoked

Disease of the coronary arteries was indicated as the primary cause of death of 2 147 men 45 6% of those on whom death certificate information was available The findings in respect to cigaret smoking were about the same as for the over all death rate except that the relationship was much more pronounced

Cancer was indicated as the primary cause of death of

844 men 18% of those on whom death certificate information was available Deaths from cancer were definitely associated with regular cigaret smoking particularly in the older age groups Approximately 26% of the total effect of cigaret smoking on the over all death rate may be attributed to the effect of cigaret smoking on deaths from cancer There may also be a relationship between cigar and pipe smoking and cancer death rates At least another year of follow up will be required before this relationship can be properly evaluated

Of the 844 deaths from cancer 167 were indicated on the death certificates as being due to lung cancer The death rate from lung cancer and also from cancer of sites other than the lung was much higher among men with a history of regular cigaret smoking than among men who never smoked regularly

The findings prove that there is a definite association between smoking habits and death rates at least in white men between 50 and 69 Most of the over all association is accounted for by an association between regular cigaret smoking and death rates from cancer and from diseases of the coronary arteries although other diseases may also be involved The associations found between regular cigaret smoking and death rates from diseases of the coronary arteries and between regular cigaret smoking and death rates from lung cancer reflect a cause and effect relationship

[This study has been so widely discussed during the past year in the lay press as well as in scientific publications as to make any editorial comments here seem almost superfluous Whether one should regard such evidence as proof or merely as a statistical association which could be misleading with respect to causal relationships can probably not be determined until the causes of cancer and of coronary artery disease have been worked out in greater detail Meanwhile the case against smoking as an important contributory causal factor in these disorders is impressive —Ed]

PNEUMOCONIOSIS

Coal Miners Pneumoconiosis Joseph E Martin Jr[4] (Memorial Gen l Hosp Assoc Elkins W Va) notes the reluctance to accept the fact of pulmonary disease related

(4) Am J P b H alth 44 581 591 M y 1954

to coal mining although it has long been known that miners die earlier than the general working population If lung sections failed to show typical nodules and x rays revealed no opacities disability or death was considered due to other than pulmonary disease

Pneumoconiosis has been defined as a diagnosable dis

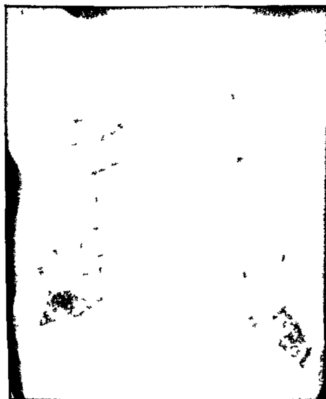


Fg 29—S t n f l ng h w g f l a um l t on f o l d t (C te y f M rt J E J Am J P b H lth 44 581 591 M y 1954)

ease of the lungs produced by the inhalation of dust the term dust being understood to refer to particular matter in the solid phase but excluding living organisms In simple pneumoconiosis there are widespread accumulations of coal dust in small foci mainly at the bifurcation of the terminal bronchioles and around small blood vessels (Fig

29) They cause little reticular-fibrosis in contrast to the abundant collagen fibrosis in silicosis

Simple pneumoconiosis makes the lung vulnerable to the more disabling and fatal progressive massive fibrosis Some factor other than inhalation of dust probably an infection



F g 30 —S mpl pn m ft l m 70 who h d w k d 34
y d g d H h d no g fi t p t ry d ffi lty S m F gu e
29 (C t y f M rt J E J Am J P b H lth 44 581 591 M y 1954)

seems necessary to produce the severe disease In progres sive fibrosis the lungs contain masses of dense black tissue varying from about 1 cm diameter up to masses occupying an entire lobe Washing brings out a fine filigree of silver gray connective tissue running through a dense black back

ground There may be cavities at the center When these areas of massive fibrosis have caused shrinkage there is often severe emphysema

Characteristic in the x ray appearance of coal miners pneumoconiosis are small more or less circular discrete



F g 31 —P og s m fib c l m r 42 wl h d w k d for 30 y s n sl m l (C t f M t J E J Am J P b Health 44 581 591 M y 1954)

disseminated opacities up to 1 mm diameter As exposure continues they increase in number size and radiologic density until the whole lung field is filled Simple pneumoconiosis is graded in three categories of severity based on increasing size and number of the opacities British investigators found that simple pneumoconiosis progresses only

when exposure to coal dust continues Progressive massive fibrosis almost always increases in severity whether or not exposure continues

Martin reports on more than 400 soft coal miners all with typical chest x ray abnormalities Of 100 consecutive



Fg 3 —Ch t y f f l m 58 wh pp d work 43 y ft t l p t l d t D p t p m fib d p t t on to d t g h I PD t b l b ll ld n t be d t m p t m (C t y f M t J E J Am J P b H lth 44 581 91 M 1954)

patients aged 20 to over 80 years most were between 40 and 69 They had started to work underground at 10 to more than 40 years of age 65% before age 20 Of 22 still working 15 had worked over 20 years and 3 over 40 years Of 39 who had stopped work because of respiratory difficulties 37 had worked underground over 20 years 39 had

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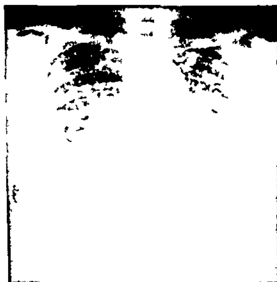


Fig 31—P ogre m e fit oal m r 4 wh h d w ked f r 30 y a n te m oal (C rt y f M t J F J Am J P I H alth 44 581 591 M y 1954)

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and William C Wycoff[7] (Pittsburgh) report a case of tin oxide pneumoconiosis

Man 73 a smelter and bagger of tin oxide for 22 years had dyspnea about 11 years later Physical examination showed a well developed and nourished man in no respiratory distress Chest was of emphysematous configuration but aside from a few rales at the bases and slight generalized depression of breath sounds no ab



Fg 33 —X y f m p d t t d powd r yea (Co rt y f Spe G E d Wy ff W C I d t Hyg & O p M d 10 295 297 Oct be 19 4)

normalities were noted Heart tones were normal and no murmur was heard Blood pressure was 178/104 and a 1+ pitting edema of both ankles was noted Liver was not enlarged Fluoroscopy disclosed generalized mottling throughout the lungs Diaphragmatic motion was restricted by adhesions X ray findings were characteristic of tin oxide pneumoconiosis (Fig 33) Electrocardiogram showed left ventricular hypertrophy Sputum was negative for tubercle bacilli Red blood cell count was 3 890 000 hemoglobin 14 Gm and white blood cell count 7 850 with normal differential count Urine was normal and sedimentation rate 22 mm/60 minutes Vital capacity was 70% of normal and maximal breathing capacity 61% of the predicted normal

(7) I d t. Hyg & O p Med 10 295 297 Oct ber 1954

By January 1952 the disease was a minor problem judging by the paucity of official occupational disease reports However the popular press called attention to the high tuberculosis death rate in areas where the earth deposits were worked A thorough environmental and medical study of the industry was initiated in California and legal requirements were issued for reduction of dust concentrations In November 1952 the first medical publication on diatomite pneumoconiosis in a major United States medical journal in 20 years appeared

Abrams found 32 claims for compensation for alleged diatomite pneumoconiosis which came before the California Industrial Accident Commission between 1930 and 1951 and 26 additional cases not in workmen s compensation files

Abrams conclusions follow (1) The disease has a high attack rate in those exposed to the dust (2) The amorphous form of the earth can cause symptomatic lung disease although not as soon as the processed powders (3) Exposure to processed diatomite results in disabling disease on the average more rapidly than does exposure to quartz type silicon dioxide (4) Diatomite pneumoconiosis probably predisposes to tuberculosis and other lung infections such as pneumonia and pneumonitis (5) It may occur in industries using diatomaceous earth as well as in those which produce it

This study indicates that workmen s compensation did not measure up well to its objectives Of the 32 claim records analyzed at least 26 in the light of present knowledge were for definite cases of diatomite pneumoconiosis Only eight claimants had received full awards when this study was concluded

[It is shocking that medical publications concerning this situation lapsed for 20 years until the disease hazard became the focus of a strike issue and its recognition was forced by publicity in the lay press Dr Abrams report is written in the form of an inquiry into some of the factors operative in the progress or lack of progress of industrial health He points out that a long time lag between the first medical publication and general recognition of an occupational disease has not occurred in this instance alone Beryllium lung disease went through a somewhat similar evolution and at the present time coal workers pneumoconiosis is awaiting general recognition as an occupational disease (see p 155) —Ed]

Benign Tin Oxide Pneumoconiosis George E Spencer

certain states and the number of reported cases Of the 101 cases 89 were in men and 12 in women Only one patient was under age 20 Average age for men was 40.6 for women 49 8 Forty six persons could be listed in a dust exposed group

Only 3 of the 101 patients died despite the fact that 52 had generalized disease A high incidence of obvious lung involvement seems to indicate that blastomycosis probably begins in this organ whether or not there are cutaneous manifestations 21 patients had lung involvement without any skin lesions

Stilbamidine and derivatives were used in 39 patients either alone or in combination with potassium iodide or other drugs In the authors experience clinical improvement following stilbamidine and 2 hydroxystilbamidine therapy seemed to be more rapid than that with iodides This was essentially the consensus of most observers

[The authors of this study mention an epidemic of blastomycosis observed in North Carolina attacking 10 persons all of whom lived within a radius of 4 miles The epidemic has been studied by J G Smith *et al* (J A M A 158 641 June 25 1955) but the publication was received too late for inclusion in this volume The report is of great interest because this is the first culturally documented epidemic of North American blastomycosis

The survey by Drs Schwarz and Goldman does not claim to represent an accurate account of all cases in the United States but it is of value in indicating the approximate distribution and frequency of the disease —Ed.]

Pulmonary Blastomycosis Critical Analysis of Medical and Surgical Therapies with Report of Six Cases Page W Acree Paul T DeCamp and Alton Ochsner[9] state that stilbamidine and 2 hydroxystilbamidine are safe and effective drugs in pulmonary blastomycosis and pulmonary resection may be employed when indicated Blastomyces dermatitidis causes cutaneous and visceral lesions with equal frequency The dermatitis is relatively benign but mortality in visceral disease has been 90% The lungs are involved most frequently then the skeletal system but lesions have been found in every organ and tissue of the body The lung is the portal of entry at least in the systemic disease Even without specific therapy there is a strong healing tendency in the lungs and it is probable that unrecognized and self limited cases have occurred

Pulmonary blastomycosis usually develops as an indolent

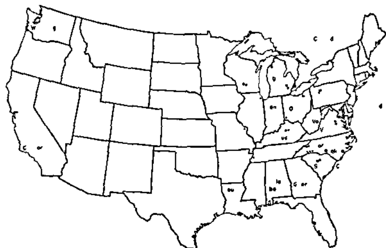
(9) J Tho S g 28 175 193 A gu t 1954

The relatively slight impairment of function with the massive x ray configuration is characteristic of the benign nature of tin oxide pneumoconiosis

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PULMONARY MYCOSES

Epidemiologic Study of North American Blastomycosis To determine the number of cases of blastomycosis observed in North America during the first six months of 1953 Jan



Fg 34—D t b tion f p t d s s f bl t my o a b d t p t one p t e t b v d d g th fi t h lf f 1953 (Cou te y f S hw J nd G ld m L A M A A ch De m t & Syph 71 84-88 Ja ry 1955)

Schwarz and Leon Goldman[8] (Univ of Cincinnati) sent questionnaires to 1 569 dermatologists and 403 chest surgeons The questions concerned the number of cases treated the methods of diagnosis utilized treatment and available follow up Answers were received from 74% of dermatologists and 51% of chest surgeons

Reports were received on 101 cases of blastomycosis most frequently diagnosed by biopsy The geographical distribution is shown in Figure 34 No relation was found between density of population or number of physicians in

(8) A M A A ch D m t & Syph 71 84 88 J n ry 1955

Positive reaction to the skin test is considered significant and the complement fixation test may give a positive response in extensive forms of the disease

The best chemotherapeutic agent known is 2 hydroxy stilbamidine because of its effectiveness and freedom from toxicity It will usually cause regression of the pathologic lesions with closure of cavities and convert the sputum responses to negative and will alleviate clinical manifestations of the disease

Patients are placed on a low protein low-purine diet during treatment because these substances antagonize the action of the stilbamidines The agents are given in freshly prepared solutions as a slow intravenous drip Increasing doses of 2 hydroxystilbamidine are given up to 0.225 Gm in an adult daily or every other day Treatment may be continuous or in discontinuous series Seabury advises 5 8 Gm for moderately extensive pulmonary disease and 8 Gm or more for patients with large areas of necrosis or abscess formation The drugs are stored for as long as a year in numerous tissues in the body and the therapeutic effect possibly is prolonged

Blastomycosis may cause extensive destruction of pulmonary tissue with abscess and cavity formation and as several authors have suggested in some instances surgical excision of residual cavities and destroyed tissues will be indicated following chemotherapy as in one of the present cases Relatively short term observations indicate that prognosis i excellent when the disease is treated with 2 hydroxystilbamidine followed by surgical resection if necessary

Acute Disseminated Histoplasmosis with Report of Case Occurring in England F C Poles and J D O D Lavertine[1] report the following case of histoplasmosis in which the infection was acquired in England

Man 45 had sore throat loss of voice and hoarseness for five months but no cough or sputum His general health was good Chest x ray showed a small calcific focus in left midzone and a few miliary deposits in right lower and left upper zones Left vocal cord was swollen friable and suggestive of neoplasm Biopsy revealed nonspecific granulation tissue with histiocytes containing yeastlike bodies resembling H capsulatum No evidence of carcinoma or tuber

(1) Tho 9 33 241 Sept mbe 1954

chronic infection causing fever malaise night sweats and weight loss and such thoracic symptoms as cough sputum hemoptysis dyspnea and chest pain The pulmonary infection may be protean in its manifestations and associated lesions in the skin subcutaneous tissues or the viscera may occur Schwarz and Baum classified the pulmonary lesions as (1) primary exudative pneumonia without granuloma formation (2) chiefly granulomatous lesions with

DIAGNOSTIC FINDINGS* IN 6 CASES OF PULMONARY BLASTOMYCOSIS TREATED BY RESECTION

CASE	X RAY	SPUTUM CULTURE FOR FUNGI	PREOP DIAGNOSIS
1	Density left apex (inflammatory)	Neg	Inflammatory disease
2	Tumor left upper lobe	Neg	Carcinoma
3	Cyst left upper lobe	Neg	Cystic disease
4	Density right upper lobe	Neg	Inflammatory disease
5	Tumor left upper lobe	Neg	Carcinoma
6	Cavity left lower lobe	Pos for blastomycosis	Blastomycosis

* Re lt of b o ho opy w gat e ll es

epithelioid cell tubercles and (3) mixed exudative and granulomatous lesions

The disease may involve the chest wall directly or by metastasis but has little tendency to cutaneous fistula formation so common in actinomycosis Generalized spread may be expected at any time the fungi having been seen repeatedly in the blood vessels the route of spread

It is difficult to identify the lung lesions of blastomycosis Preoperative diagnosis was made in only one of six reported cases (table)

There is no characteristic roentgen pattern Every type of picture from widespread bilateral disease to solitary coin lesions has been seen Since the disease is a granuloma it must be differentiated from tuberculosis coccidioidomycosis moniliasis histoplasmosis and torulosis

Smear and culture of the sputum are ideal for making a positive diagnosis *Unstained pus particles from the sputum* liquefied by potassium hydroxide frequently reveal typical organisms

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6	Cavity left lower lobe	Pos for blastomycosis	Blastomycosis

* Results of bronchoscopy were negative in all cases

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scopically yeastlike cells were found in granulation tissues of larynx lungs and adrenals No acid fast bacilli were recovered

Once histoplasmosis has been suspected clinically it should be possible to confirm the diagnosis histologically or by culture In this case the final diagnosis rested on histo logic grounds Yeasts were seen within reticuloendothelial cells and also free in the tissues The morphology of the fungus was best demonstrated by Giemsa s stain

Pulmonary Histoplasmosis in Farm Family Three Year Follow up C G Loosli J J Procknow F Tanzi J T Grayston and L W Combs[2] (Univ of Chicago) have ob served over a period of three years the changing clinical and laboratory findings in six members of a family who had pulmonary infections due to Histoplasma capsulatum The father had a severe prolonged illness during which the fungus was isolated from sputum and bone marrow Two sons had acute extensive but less severe pulmonary infec tions the daughters and oldest son had lesser pulmonary involvement and no symptoms Diagnosis was made by a combination of procedures including culture complement fixation test using yeast phase antigen and skin test with histoplasmin coccidioidin and tuberculin antigens

With recovery the complement fixation reaction became negative and reactions to the skin tests with histoplasmin have been consistently positive The father and mother have also reacted positively to tuberculin since January 1952 None have reacted to coccidioidin The extensive dissemi nated infiltrates in the lungs of the father and two sons have undergone healing by fibrosis and calcification Cal cification occurred most rapidly in the youngest son and most slowly in the father The lung infiltrate in one daugh ter healed by resolution those in the other daughter and oldest son were essentially unchanged

The source of H capsulatum on the farm was a silo which was cleaned by the father and his two sons three weeks before onset of their illness The cases are the first in which the source of the histoplasma fungus which caused the infection was readily found in the immediate environ ment

(2) J L b & Cl M d. 43 669 695 M y 1954

culosis was seen Hemoglobin content was 80% erythrocytes 4 120 000 and leukocytes 2400 Reaction to an intradermal histoplasmin test 1 100 was negative No fungi were recovered from the bone marrow

A few weeks later patient began to have fever lassitude loss of weight cough dyspnea and intermittent diarrhea Spleen was en larged and liver edge was palpable Mantoux and histoplasmin tests caused negative reactions Chest x ray showed generalized mottling He was given streptomycin and sodium para amino salicylic acid Diarrhea ceased and spleen decreased in size during



F g 35 (l ft) —X h w n xt ft h d w b g co fl t at ght b
Fig 36 (ght) —D t l f h d w h w m k d a a
(Co te y f P l s F C d L t e J D O D Th x 9 233 41 September 1954)

the first weeks of treatment He then began to deteriorate rapidly X ray showed mottling throughout both lung fields there was no obvious hilar adenopathy (Figs 35 and 36) The spleen started to enlarge again There were still no palpable lymph nodes He be came disoriented blood pressure and chloride levels fell and he died suddenly

At necropsy the larynx was ulcerated Lungs showed miliary yellowish gray nodules becoming confluent in the lower lobes There was little fibrosis but no cavitation Tracheobronchial lymph nodes were slightly enlarged without caseation Spleen was considerably enlarged with a normal cut surface The adrenals were enlarged and replaced almost entirely by necrotic granulation tissue Micro





Γg 37 (top) — A t m l y p d 3 w k ld f t de th x week
Fg 38 (bott m) — W dg hap d d n ty l ft 3d t i r i t p n p im ty
s mptomat occ d 1 m
(Court y f L J W Am J Roentg 1 72 556 573 O tobe 1954)

Roentgen Aspects of 500 Cases of Pulmonary Coccidioidomycosis J W Birsner[3] (Bakersfield Calif) studied pulmonary coccidioidomycosis in 500 patients aged 3 weeks to 77 years The diagnosis was confirmed by complement fixation test and/or microscopic presence of spherules

Among 124 children there were 26 cases of dissemination (Fig 37) but only 7 deaths In children the entity is evidently a benign condition There were five cases of cavitation which ultimately resolved The concomitancy of coccidioidomycosis and tuberculosis did not affect morbidity or mortality in either condition

In the adult coccidioidomycosis is tracheobronchial as well as parenchymal Among 352 patients aged 14 60 there were 67 cases of dissemination with 44 deaths The complications of pulmonary coccidioidomycosis are (1) fibrosis of varying degrees of parenchymal infiltration (2) coccidioma (3) dissemination (4) pleural effusion (5) bronchiectasis and (6) cavitation (Figs 38 42)

Among 24 patients over 60 10 cases of dissemination and 6 deaths were observed In this age group it is important to differentiate coccidioidomycosis from bronchogenic carcinoma

Result of a skin test is of little significance in an acute illness If the reaction is positive it may be due to previous infection if it is negative the test may have been initiated too early It is frequently negative in all dilutions if dissemination has occurred The test is significant if the reaction is negative first and becomes positive two to three weeks later

Pulmonary complications that are problems in diagnosis are persistence of hilar shadow enlargement and coccidioma Over 90% of coccidiomas are located more than 5 cm from the hilar area and their average diameter is 1 3 cm

In all cases of dissemination the process occurred within nine months after the initial symptoms the average being three to five months Except for the relation between miliary spread and dissemination degree and incidence of pulmonary complications apparently cannot be correlated with dissemination predictions

There is no known treatment for primary coccidioidomycosis During the acute stage antibiotics are recommend

(3) Am J Roentgenol 72 556-573 Oct ber 1954



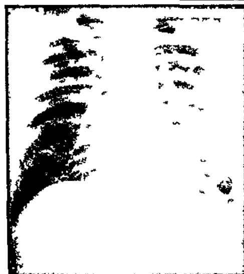
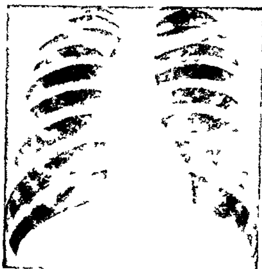


Fig 41 (t p) —L g tv w th fl d l l y ft f l p mo-pe t

Fig 42 (bott m) —H l den p th w th filt t on phy d m a ea w k

(Court y f B J W Am J Roe tgen l 72 556 573 O t be 1954)





F g 39 (t p) —M ltuple oc d m
F g 40 (b ttom) —Coc d d l tat on a oc at d fib d b b ectas a
(C u t y f B n J W Am J Roe tg 1 32 556 573 O t b 1954)

ture was 98 6 F pulse rate 80 and blood pressure 114/80 There were diminished resonance with increased breath sounds over the right upper lobe posteriorly and wheezes and rhonchi throughout the chest Roentgenograms showed consolidation of the subapical segment of the right upper lobe (Fig 43) There were marked weakness with areflexia of the right arm and leg and abnormal extensor plantar response on the right A slow wave focus in the left motor area was present in the EEG

At craniotomy a round firm encapsulated mass in the precentral gyrus 1 1 5 cm below the surface was removed The operative field was irrigated with penicillin solution before closure Pus from the abscess contained a few gram positive and gram negative non acid fast rods Culture yielded a filamentous aerobic gram positive non acid fast fungus identified as nocardia also cultured from a sputum specimen on the 12th postoperative day

In vitro tests proved sensitivity to chlortetracycline chloramphenicol streptomycin and oxytetracycline and resistance to penicillin In six weeks 80 000 000 units of penicillin and 75 Gm chlortetracycline were given

Function in the fingers hip and knee returned and in a month he could walk with support In a week the density in the chest film began to clear Two months later there were a few linear fibrotic strands in the periphery of the right midlung which remained unchanged (Fig 44) A sputum specimen eight months after surgery yielded nocardia on culture although later cultures did not The main neurologic residual was right sided hemiparesis

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SARCOIDOSIS

Nickerson Kveim Reaction in Sarcoidosis Louis E Siltzbach and Joseph C Ehrlich[5] (New York) tried the Nickerson Kveim cutaneous test for sarcoidosis in their studies The test consists in the intradermal injection of a heat sterilized suspension of human sarcoid tissue and subsequent histologic examination of the site of injection In a positive reaction a sarcoid like granuloma is produced at the injection site after some weeks

The test was given to 200 patients Fifty eight had sarcoidosis the diagnosis being confirmed by biopsy of an involved organ or tissue Eighty were sarcoidosis suspects 33 of them strong suspects Fifty four had diseases other than sarcoidosis and they served as controls Eight had unclassified granulomatous disorders A high percentage of the biopsy confirmed group and of the strongly suspected group

(5) Am J M d 16 790 803 J 1954

ed In the treatment of residual pulmonary complications thoracic surgery should be performed if warranted When pleural effusion occurs thoracentesis is indicated Positive confirmation is needed in all cases of suspected coccidioido mycosis and cases of erythema nodosum with or without associated pulmonary hilar adenopathy should be checked for possible coccidioidal origin The disease should be con sidered an occupational hazard in an endemic area

Nocardiosis of Central Nervous System Erich G Krue ger Luigia Norsa Michael Kenney and Pliny A Price[4]



F g 43 (l ft) —Che t x y n b p t h t o h w g con l dat on n ight upp r l be
F g 44 (r ght) —E ght months aft p t on d t e tme t n t lear g of s l dated a e
(C u te y f K g r E G t l J Ne g 11 226 33 May 1954)

(V A Hosp Bronx N Y) state that pulmonary involve ment in nocardiosis is the commonest clinical manifesta tion often simulating tuberculosis Involvement of the cen tral nervous system usually in the form of brain abscesses and reported in about 30% of cases of nocardiosis often seemed directly responsible for death The authors report a patient alive and well 15 months after excision of a nocardia brain abscess

Man 42 was hospitalized with a four day history of sudden right sided hemiparesis There had been no fever or weight loss but he had had a chronic cough productive of grayish white spu tum for eight years

He was well developed and did not appear acutely ill Tempera

(4) J N o o u g 11 226 233 May 1954

tered progressive sarcoidosis caused death of four patients

Cortisone is indicated for patients with ocular lesions increasing x ray changes or debilitating symptoms and may safely be given when diagnosis of sarcoidosis is supported by careful studies The pattern of response to cortisone in sarcoidosis is not characteristic of infections or collagen disorders

Isoniazid and PAS in Chronic Pulmonary Tuberculosis A Warning C L Joiner K S MacLean J D Carroll K Marsh Patrick Collard and Robert Knox[7] (Guy s Hosp London) compared the therapeutic effect of 250 mg isoniazid and 10 Gm para aminosalicylic acid (PAS) daily given continuously for 24 weeks with that of rotating pairs of isoniazid PAS and streptomycin (1 Gm intramuscularly twice weekly) every 4 weeks Comparable groups of 13 and 14 patients with chronic fibrocaseous pulmonary tuberculosis were treated

Initial improvement followed by clinical and bacteriologic relapse was seen with continuous isoniazid and PAS therapy and was associated with emergence of strains of organisms resistant to both drugs Progressive improvement was seen with rotating pairs of drugs

Courses of chemotherapy for tuberculosis must be long Follow up of patients with chronic fibrocaseous pulmonary tuberculosis with negative sputum after various courses of chemotherapy has shown that even with six months continuous treatment relapse rates are as high as 75% Thus a combination of drugs that continues effective for as long as possible should be selected This study suggests that isoniazid and PAS in the dosage given is not such a combination

TUBERCULOSIS

The past year has been one of considerable disagreement and uncertainty bordering even on confusion regarding the treatment and general management of tuberculosis Not only do problems concerning the choice of drug regimens and the indications for excisional surgery remain controversial and unsettled but the time honored standards of rest and institutional care are being questioned and are gradually undergoing modification Such a period of reorientation is inevitable in view of the outstanding success of the drug therapy of the disease and it will require

(7) La et 2 663 666 O t 2 1954

gave histologically positive responses to the test i e 86% of the former and 85% of the latter Two patients in the control group had positive responses an incidence of 4% of false positive reactions

Biopsy of the injection site was considered an obligatory part of the intracutaneous test It was usually carried out four to six weeks after the sarcoid suspensions were injected In all 571 biopsies were performed A result was called positive only if a histologically characteristic sarcoid like granuloma could be demonstrated at the site of injection Foreign body and nonspecific reactions sometimes interfered with the microscopic reading of the test Suspensions of normal lymph node and normal spleen did not evoke a positive reaction in patients with sarcoidosis who did respond to a suspension of sarcoid tissue

The Nickerson Kveim intracutaneous test is useful in the diagnosis of sarcoidosis especially when tissues from involved organs are not readily accessible to biopsy It is also used in differentiating granulomatous conditions In such instances the result can also be a determining factor in the choice of proper therapy

Cortisone Treatment of Sarcoidosis Experience with 36 Cases is reported by Harold L Israel Maurice Sones and Dick Harrell[6] (Philadelphia) Most patients received 200 mg cortisone daily for 10 days followed by outpatient treatment In 11 dosage was rapidly reduced and discontinued 19 with chronic disease received gradually diminishing doses over one to four months to a total of 3 10 Gm and 5 with severe respiratory disability were treated for one to two years Results were judged by x ray and clinical criteria and occasionally by respiratory function studies

Cortisone had a consistently favorable symptomatic effect in sarcoidosis Improvement in pulmonary x ray signs was inconsistent and mediastinal adenopathy was not affected Benefit was most striking in patients with extra pulmonary manifestations (ocular parotid cutaneous or myocardial) and in those with symptoms of brief duration The long term effect of cortisone was less impressive suggesting that in many cases the course of the disease has not been altered No instances of tuberculosis were encoun

(6) J A M A 156 461-466 Oct 2 1954

In some respects the crucial period of tuberculosis is during its early phases when resistance to the infection may increase to suppress it completely In the case following recent primary infection specific acquired immunity seems to ri e slowly during a year or so There is a significant correlation between respon e to treatment during the first two years and later prognosis (table) If the minimal lesion remains within its bounds or diminishes dur

RESULTS OF TREATMENT OF MINIMAL TUBERCULOSIS IN STUDENT NURSES

1 Disease considered clinically stable after 2 yr of treatment (9 with pneumothorax now re expanded)				65
Relapses with subsequent recovery			7	
Status in 1952				
Dead		3		
from tuberculosis	0			
from anesthesia relate i to surg ry for tuberculosis	1			
suicide	2			
Under treatment		0		
Living and well		62		
		65		
2 Disease considered clinically unstable at the end of 2 yr of treatment				25
Relapse or chronically active clinical course			17	
Status in 1952				
Dead		4		
from tuberculosis	3			
from ane thesia related to surgery for tuberculosis	1			
Under treatment or limited in activity		13		
Living and well		8		
		25		

I od f b rv t 5 0 y a

ing this period the rate of relap e is low On the other hand lesions still unstable at the end of two years frequently remain so and the rate of relapse is high in a few cases the disease goes on to a fatal ending In many cases the outcome is probably foreshadowed within the first few months

The use of specific chemotherapeutic agents including streptomycin isoniazid para aminosalicylic acid and viomycin so modifies the course of pulmonary tuberculosis that new question arise When streptomycin alone was used an important limitation was the predominance after several months of treatment of drug resistant strains of the

some time before the optimal condit on are determined Possibly the modifications and shortening of rest t eatment are proceeding too rapidly but if so this is not yet reflected either in a slowing of the rapid rate of decline in mortality or in any definite increase in morbidity On the con trary the trends appear to be continuingly favorable Alarm is expressed in some quarters concerning so called ambulatory treatment but the organized programs of outpatient treatment are in actuality concerned in largest part with pre and post hospital treatment rather than with a planned replacement of hospital care by outpatient care except where hos pital care is unavailable or for those who refuse it Most authorities now agree that when hospitalization must be delayed for any reason or when it is unavailable active drug therapy should nevertheless be instituted promptly The need for prolonged pre hospital treatment however is diminishing in most sections of this country as the hospital waiting lists are rapidly disappearing Initiation of treatment in the hospital of all open sputum positive cases is considered advisable by virtually all au thorities from both public health and therapeutic standpoints There is wide divergence of opinion concerning the continuing need for prolonged bed rest but as yet little actual information is recorded concerning whether it may safely be dispensed with for optimal results One provoc ative study on this subject by Dressler *et al* will be found on page 194

The following selections are mostly concerned with treatment They reflect the predominant current concern among students of the disease with this aspect of the problem either directly in the clinic or indirectly in the laboratory Numerous different approaches and divergent points of view are represented To keep the whole subject in balance and to disabuse those who would hastily dismiss tuberculosis as no longer a major therapeutic problem the first article in the following group by a foremost student of tuberculosis is particularly recommended—Ed

Evolution of Pulmonary Tuberculosis and Its Behavior under Treatment is discussed by J Burns Amberson[8] Current changes in treatment of tuberculosis are attributed to progressive improvement of diagnostic methods dis covery of specific antibacterial drugs widening scope of thoracic surgery and clearer understanding of the patho genesis of the disease The results achieved have engendered a degree of optimism among patients and physicians which sometimes exceeds reason

Tuberculosis is treated much the same as nontuberculous necrosing inflammation at least during the early phase when specific drugs and measures to promote resistance of the body are used *Beyond this point however the path diverges* because of long survival of the tubercle bacillus in the tissues slowness of softening and sloughing of the necrotic lesion which tends to be sequestered and retained in the lung as an ever threatening focus and transmission of virulent infection to the other parts when sloughing does occur

(8) Bull J hns Hopk n H p 94 337 347 J 1954

elastic parenchyma as the cavity tends to collapse A striking feature after some weeks or months of chemotherapy is the disappearance of sputum and the failure to recover tubercle bacilli in cultures of specimens while the cavity remains This effect has raised the question of whether cavities while still open may undergo substantial or complete healing Although the walls of some of these cavities consist largely of clean fibrous tissue with extension of bronchial epithelium over small parts of their surface elements of tuberculosis persist in most of them ruling out the theory of complete open healing

The drying effect of chemotherapy often averts spread of infection and confines the bacillus until the lesion closes or can be eliminated surgically With abatement of the destructive process hemorrhages from cavities during chemotherapy are also relatively infrequent

The change of the growth characteristics of tubercle bacilli obtained from solid and semisolid necrotic lesions treated with drugs requires further study Dubos and others have expressed skepticism that all these organisms which are morphologically intact but sometimes fail to grow in artificial culture mediums and to infect guinea pigs are dead Relapses after long periods of apparently effective chemotherapy indicate that the lesions have not been sterilized When patients do well after discontinuance of chemotherapy it seems more reasonable to give credit to their resistance

An important question is whether healing under rest treatment alone is as favorable and durable as that achieved with addition of chemotherapy Under the latter healing is accelerated and the vital properties of tubercle bacilli are presumably changed at least temporarily Little is known however about the state of vital resistance except that it seems to vary in different cases The fact that such differences appear less frequently when chemotherapy is continued for a year or more indicates that artificial suppression of the infection not only holds the disease in abeyance but increases resistance

Chemotherapy has strikingly increased the degree of safety with which diseased pulmonary tissue may be removed The timing of surgery is important While some

tubercle bacillus which overran the field of disease and often continued the destructive process The discovery that simultaneous administration of two or more different drugs of this group helps to inhibit proliferation of resistant strains opened the way for prolonged treatment

The effect of chemotherapy on pulmonary lesions has not been found to differ greatly from that of natural resistance except in degree and rate With the rest cure or chemotherapy the first favorable response is subsidence of active inflammation reflected in alleviation of general symptoms of toxemia halting of the extension of lesions demonstrated by x ray and diminution of exudation These changes however are generally more rapid under chemotherapy In highly acute caseous pneumonia for instance six or eight weeks or even more may pass before the severe inflammation comes to a halt under rest treatment alone most of the lesions progress without interruption

The effect of chemotherapy in stopping necrosis in existing lesions is not clear The best assurance of this effect is in the demonstration of resolution Although necrosis may take place in any part of an exudative lesion the process is prevented in areas in which resolution intervenes However while resolution of exudate about the periphery of a lesion may occur the necrotic center may continue to undergo liquefaction and excavation The same phenomenon is sometimes seen in patients not treated with drugs but appears to be less striking Excavation occurs most conspicuously in acute cases in which extensive caseation has taken place presumably before the start of treatment In other cases usually more mild chemotherapy seems to arrest sloughing and the caseous matter may become inspissated

After evacuation of its necrotic contents a pulmonary cavity tends to shrink more rapidly under chemotherapy Shrinkage may occur early and may be favored by resolution of edematous inflammatory lesions of the mucosa of communicating bronchi Abatement of this obstruction improves ventilation releases partly trapped air which may have distended the cavity and facilitates drainage of purulent exudate at the same time resolution of lesions about the wall of the cavity may allow freer movement of the

had no preoperative chemotherapy or had patent open cavities at the time of resection

It is apparent that tubercle bacilli can survive in healed or semihealed necrotic pulmonary lesions even after prolonged chemotherapy

Clinicopathologic Significance of Demonstration of Viable Tubercle Bacilli in Resected Lesions is discussed by Oscar Auerbach Gladys L Hobby Maurice J Small Tulita F Lenert and John V Comer[1] who correlated clinicopathologic and microbiologic observations on resected tuberculous lesions from 19 patients Four of the patients were considered as controls 14 had received 4 12 months of chemotherapy preoperatively and had morphologic evidence of cavity closure and 1 had 11 months of chemotherapy preoperatively and showed evidence of an open cavity with healing Viable tubercle bacilli were recovered from the 4 controls and also from 11 of the 15 original and retreated patients

Most of the patients received streptomycin twice weekly in combination with PAS daily Five received isoniazid daily together with streptomycin or PAS

No correlation between presence of viable tubercle bacilli in tuberculous lesions and duration of chemotherapy drug regimens used duration of preoperative period noninfectiousness or anatomic nature of the lesions could be demonstrated

Judged by these findings inspissated cavities with communicating bronchi are potentially dangerous in a high percentage of cases after prolonged chemotherapy on regimens universally used today

[Drs Hobby Auerbach and their associates present in the foregoing two articles evidence of the long term viability of tubercle bacilli after antimicrobial therapy which is at variance in some respects with the results of others notably D Esopo and Steenken who have attempted to culture bacilli from resected pulmonary lesions The character and duration of the preoperative therapy differed in some part culars from that received by D Esopo s and Steenken s patients but not sufficiently to account for the very much higher rate of recovery of viable bacilli The principal factor was undoubtedly the *method* of prolonged incubation. Nevertheless the earlier observations are confirmed to the extent that in many instances morphologically normal bacilli d d not infect gu nea pigs on direct inoculation and could not be cultured by conventional technics The authors conclusions concerning the clinical significance of their findings in terms of the danger of reactivation of certain lesions from

(1) J Thor ic S g 29 109 135 F bruary 1955

lesions may seem well localized and fit for resection after a few weeks of chemotherapy it may be better to allow more time for improvement of the patient s resistance Except for early minimal lesions it must be assumed that infection has spread to other parts of the lungs and often elsewhere These secondary foci may be small and capable of healing permanently but their potentialities should not be ignored The period of postoperative treatment should also be determined carefully Some patients with limited chronic disease for two years or more have returned to part time work with apparent safety after three to six months of convalescence and chemotherapy However those with acute widespread disease sufficiently controlled to warrant surgery are usually advised to continue on a regimen of rest and chemotherapy for six months to a year before resuming their usual activities

Late Emergence of M Tuberculosis in Liquid Cultures of Pulmonary Lesions Resected from Humans Gladys L Hobby Oscar Auerbach Tulita F Lenert Maurice J Small and John V Comer[9] report bacteriologic observations on *31 resected tuberculous lesions from 19 patients* Mycobacterium tuberculosis was recovered from 25 of the 31 lesions In 9 of the 25 viability was first detected only after incubation for more than 9 12 weeks All strains of M *tuberculosis recovered from the lesions were highly virulent* for guinea pigs although only 10 of the 25 lesions showing growth were capable of producing tuberculosis on direct inoculation into guinea pigs

Fourteen of the 19 patients had received chemotherapy for 4-12 months preoperatively and had morphologic evidence of cavity closure Strains of M tuberculosis were grown from 21 of 27 closed or healed lesions Although prolonged incubation was necessary for detection of viable tubercle bacilli in lesions from patients who had had repeated cour es of chemotherapy no correlation was observed between length of preoperative course of chemotherapy or period of preoperative noninfectiousness and frequency with which *viable tubercle bacilli were detected*

Growth of M tuberculosis was readily demonstrated on cultivation of four lesions from control patients who either

(9) Am Re T berc 70 191 218 A gu t 1954

had no preoperative chemotherapy or had patent open cavities at the time of resection

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(1) J Th S g 29 109 135 F bru ry 1955

which viable bacilli are recoverable are somewhat speculative This is tacitly recognized for they wisely refrain from engaging directly in the controversy concerning whether closed residual lesions should or should not be resected —Ed]

Effect of Antimicrobial Therapy on Prognosis of Primary Tuberculosis in Children is discussed by Edith M Lincoln Specific therapy has markedly reduced mortality among children admitted to Bellevue Hospital New York with primary pulmonary tuberculosis Mortality for 1930-46 was 21 5% It fell to 5% after introduction of streptomycin combined with promizole® or para aminosalicylic acid even though only 35% of patients received antimicrobial therapy *Since the introduction of isoniazid (1952) mortality rate* has been reduced to 1 5%

There is evidence that isoniazid may prevent the development of complications of primary tuberculosis especially meningitis

Of 65 patients with meningitis treated in 1947 53 45 survived no relapses occurred later than six weeks after discontinuing streptomycin Most of the children lead normal lives usually after long periods of convalescence Four have residual hemiparesis Diminution or loss of hearing occurred in about a third Final evaluation of psychiatric and psychologic prognosis should be made only after adequate periods of observation

Following specific treatment many children show apparently complete regression of tuberculous bronchopneumonia with disappearance of the primary cavity in roentgenograms and remission of all clinical symptoms Cures should not be assumed however until a long period of observation after cessation of chemotherapy has failed to show roentgen or clinical evidence of relapse

Isoniazid in Treatment of Primary Pulmonary Tuberculosis R McLaren Todd[3] (Univ of Liverpool) attempted to assess the value of isoniazid in children with primary pulmonary tuberculosis Alternate patients in a series of 50 were given 3 mg /lb body weight/day for three months Treated children had a better clinical response than controls particularly as regards appetite After three months x rays showed improvement in 14 of the 24 patients re

(2) Am. Re Tuberc 69 682 689 May 1954
(3) La cet 1 794 796 Apr 16 1955

ceiving isoniazid as compared with only 8 of 26 controls However after six months and after one year there were no differences between the two groups Two treated patients aged 6 and 7 showed x ray evidence of rupture of a caseous gland into a bronchus confirmed by broncho copy After the caseous material was removed both made an uninterrupted recovery In one control aged 16 weeks when first seen tuberculosis of the left hip developed 18 months later although the primary lesion had healed by calcification

In children over age 3 serious complications are uncommon but if they do arise it is usually within three months of development of the primary tuberculous complex Although the ultimate prognosis judged on clinical grounds and on the appearance of calcification was similar in the two groups it appeared that isoniazid therapy was more often associated with a decrease in size of the primary lesion during the first three months of the illness and this is at a time when the danger of developing serious complications is greatest A larger series of patients will have to be studied to find out if this impression is correct

V Report on 32 Week Observations on Combinations of Isoniazid Streptomycin and Para Aminosalicylic Acid is made by the U S P H S Co-operative Investigation of Antimicrobial Therapy of Tuberculosis[4] The therapeutic and toxic effects observed in a study comparing the usefulness of two dosage levels of i oniazid and of various combinations of isoniazid with streptomycin and para aminosalicylic acid (PAS) are discussed Streptomycin was given in doses of 1 Gm twice a week PAS 10-12 Gm daily and isoniazid 3 or 10 mg /kg body weight

Of 1,284 patients who had not had previous antimicrobial therapy 768 remained under treatment for 32 weeks Nearly a seventh of those given a daily dose of 10 mg isoniazid/kg body weight could not tolerate that dose although little toxicity appeared with the 3 mg /kg dose Regimens using the lower dose of isoniazid produced roentgenographic clearing and symptomatic improvement as frequently as the higher dose

Comparison of results achieved with isoniazid in var

(4) Am. Rev T ber 70 521 526 September 1954

ious combinations with streptomycin and PAS gives no clear indication that any combination is superior The choice of agents as partners for isoniazid must be made on grounds other than therapeutic effectiveness Although streptomycin is more powerful than PAS one is as effective as the other with isoniazid If the current rejection of isoniazid alone persists then the lesser risk in combined therapy may be to use PAS with isoniazid and to reserve streptomycin for later use

In this series the combination of all three drugs for nearly eight months of treatment showed no advantage over only two Although the study provides no justification for the triple combination in previously untreated cases of recent origin deliberate selection of cases may have excluded the very patients for whom three drugs might be more effective The possibility is suggested by the high percentage of each group showing roentgen improvement during treatment When most patients improve on two drugs small opportunity remains for three drugs to demonstrate any superiority

Various Combinations of Isoniazid with Streptomycin or with PAS in Treatment of Pulmonary Tuberculosis are discussed in the Seventh Report to the Medical Research Council by Their Tuberculosis Chemotherapy Trials Committee In the final stage of a clinical trial of isoniazid for pulmonary tuberculosis 588 patients were studied in 51 hospitals 182 were treated with 1 Gm streptomycin daily plus 100 mg isoniazid twice a day, 142 with 1 Gm streptomycin twice a week plus 100 mg isoniazid twice a day 159 with 5 Gm PAS sodium salt four times a day plus 100 mg isoniazid twice a day and 105 with 5 Gm PAS twice a day plus 100 mg isoniazid twice a day When submitting a case the physician did not know which treatment the patient would receive

Based solely on results at three months it was concluded that 1 Gm streptomycin daily plus 200 mg isoniazid daily is the most effective of the four treatments and the most effective combination studied at any stage of the trial Streptomycin 1 Gm twice a week plus 200 mg isoniazid daily is less satisfactory in preventing emergence of isonia

(5) Brit. M J 1 435-445 Feb 19 1955

zid resistant organisms and cannot be recommended as a primary chemotherapeutic measure PAS plus isoniazid proved effective although not quite so powerful as strepto mycin daily plus isoniazid There is small choice between the clinical and bacteriologic efficacy of 20 and 10 Gm PAS (sodium salt) daily plus 200 mg isoniazid daily either combination providing a valuable oral chemotherapy

Chemotherapy of Pulmonary Tuberculosis with Pyrazinamide Used Alone and in Combination with Streptomycin Para Aminosalicylic Acid or Isoniazid William S Schwartz and Ralph E Moyer[6] (V A Hosp Oteen N C) treated 181 patients for periods up to 16 months Pyrazinamide used alone in a dosage of 2 8 Gm daily was effective although for only a short time Streptomycin 1 Gm twice weekly or para aminosalicylic acid (PAS) 12 Gm daily with 3 Gm pyrazinamide daily did not enhance the effectiveness of pyrazinamide or streptomycin or delay the emergence of PAS resistant or streptomycin resistant tubercle bacilli

Chemotherapy with pyrazinamide and isoniazid was found to be effective and at least the equal of any combination of streptomycin PAS or isoniazid in use at present Despite reported toxicity the low incidence of jaundice (in 2 of 181 patients) encountered in this series suggests that the combination of pyrazinamide and isoniazid be used more widely in treatment of tuberculosis particularly in streptomycin resistant cases

[On the basis of published reports of 355 patients treated with pyrazinamide alone or in combination with other drugs the incidence of icteric hepatitis related principally or entirely to this agent is 3 4% Fatalities have occurred in approximately 10% of those who had such hepatotoxic reactions Studies are in progress (Muschenheim *et al* Am Rev Tuberc 70 743 1954) relative to the possibility of reducing this risk by administering pyrazinamide in lower dosage Preliminary evaluations suggest that lowering the dose reduces but does not eliminate the risk while it does materially impair the efficacy —Ed]

Changes in Isoniazid Resistance of Tubercle Bacilli after Cessation of Treatment The Laboratory Subcommittee of the Tuberculosis Chemotherapy Trials Committee Medical Research Council[7] reports follow up data on patients with pulmonary tuberculosis who had been treated with isoniazid alone

Two groups of patients were studied One group had

(6) Am R T be 70 413 422 S pt mbe 1954
(7) Th x 9 54 259 Dec mbe 1954

received 200 mg isoniazid daily for three months and was then followed for nine months without isoniazid. The other had received 200 mg daily for six months and was followed for a further six months without isoniazid. Results of sensitivity tests were available at the beginning and the end of the follow up period for 23 patients in the first group and for 14 in the second group.

When treatment with isoniazid stopped, 16 of the 42 strains from these patients showed resistance at the highest level (growth on 50 µg isoniazid/ml), 24 showed a lower degree of resistance and 2 were sensitive. At the end of the follow up period the strains from some patients were resistant at a higher level than previously and those from others were resistant at a lower level. Of the 42 strains 10 showed resistance at the highest level and 29 at lower levels and 3 were sensitive. Over a period of at least six months there was little evidence of general reversion of resistant strains either to a lower level of resistance or to sensitivity.

Quantitative Observations on Pattern of Emergence of Resistance to Isoniazid. Ralph Tompsett[8] (New York Hosp Cornell Med Center) reports that in patients with tuberculosis who are treated with isoniazid and continue to discharge tubercle bacilli there may be evidence of drug resistance in some of the bacilli isolated. All wild type strains of tubercle bacilli, although predominantly susceptible to isoniazid, contain relatively large numbers of drug resistant mutants. During therapy a change in bacterial population is detectable as an increase in the more resistant bacteria. When isoniazid is the sole therapy this shift in bacterial population is undoubtedly rapid and of considerable magnitude.

Nearly all observations of this process have been carried out by methods involving direct culture of specimens or inoculation of a subculture in a series of solid culture mediums containing graded concentrations of isoniazid. After appropriate incubation the growth in each concentration is estimated and compared with that of the control. These methods are satisfactory for routine use but are only semiquantitative.

Tompsett attempted to determine more accurately the

(8) A R v Ty[illegible] 101 J ly 1954

quantitative aspects of emergence of isoniazid resistance to learn whether a high degree of resistance occurs with regularity The cultures studied were chosen from strains of tubercle bacilli isolated from sputum or gastric aspirate of 47 patients with pulmonary tuberculosis treated solely with isoniazid In all strains had been isolated before treatment and on at least two occasions a month or more after therapy was initiated These criteria included patient with the poorest response to therapy and with maximal opportunity for development of bacillary resistance

All cultures obtained after therapy had an increased number of resistant cells In general cells resistant to 0 1 µg isoniazid/ml showed rapid increase With two exceptions most of the cells were soon resistant to this low concentration

In some instances mutants resistant to 1 µg isoniazid ml reached 50% or more after two or three months of therapy and continued to increase In other instances they showed a similar increase then appeared to level off at 10-30% of the total population In seven cases no more than 30% of the cells were resistant to 1 µg isoniazid and generally a much lower percentage of variants was found In three instances mutants resistant to 10 µg consistently made up more than 10% of the total population In only two cultures did mutants reach levels of more than 1% of the total population

Quantitative observations on the cultures reveal the complexity of the process of change with respect to isoniazid resistance and emphasize the need for caution in drawing conclusions about the time required for neutralization of drug effect Although high degrees of bacterial resistance may occur early in therapy this is not invariable

Public Health Significance of Tubercle Bacilli Resistant to Isoniazid Daniel Widelock Lenore R Peizer and Sarah Klein[9] state that there seems to be a definite loss of virulence of isoniazid resistant tubercle bacilli if the guinea pig is the host However they found that isoniazid resistant tubercle bacilli multiply and produce tuberculous lesions in guinea pigs under proper conditions such as concomitant enteritis In view of this observation and because the spu

(9) Am J P b H Jih 45 79 83 J n rv 1955

received 200 mg isoniazid daily for three months and was then followed for nine months without isoniazid The other had received 200 mg daily for six months and was followed for a further six months without isoniazid Results of sensitivity tests were available at the beginning and the end of the follow up period for 23 patients in the first group and for 14 in the second group

When treatment with isoniazid stopped 16 of the 42 strains from these patients showed resistance at the highest level (growth on 50 µg isoniazid/ml) 24 showed a lower degree of resistance and 2 were sensitive At the end of the follow up period the strains from some patients were resistant at a higher level than previously and those from others were resistant at a lower level Of the 42 strains 10 showed resistance at the highest level and 29 at lower levels and 3 were sensitive Over a period of at least six months there was little evidence of general reversion of resistant strains either to a lower level of resistance or to sensitivity

Quantitative Observations on Pattern of Emergence of Resistance to Isoniazid Ralph Tompsett[8] (New York Hosp Cornell Med Center) reports that in patients with tuberculosis who are treated with isoniazid and continue to discharge tubercle bacilli there may be evidence of drug resistance in some of the bacilli isolated All wild type strains of tubercle bacilli although predominantly susceptible to isoniazid contain relatively large numbers of drug resistant mutants During therapy a change in bacterial population is detectable as an increase in the more resistant bacteria When isoniazid is the sole therapy this shift in bacterial population is undoubtedly rapid and of considerable magnitude

Nearly all observations of this process have been carried out by methods involving direct culture of specimens or inoculation of a subculture in a series of solid culture mediums containing graded concentrations of isoniazid After appropriate incubation the growth in each concentration is estimated and compared with that of the control These methods are satisfactory for routine use but are only semi quantitative

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(8) Am R T bc 70 91 101 July 1954

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(9) Am J P b H lth 45 79-83 J uary 19 5

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(8) Am R T b rc 70 91 101 J ly 1954

itself primarily in a significantly decreased incidence of progressive bronchogenic spreads of tuberculous infection in patients receiving isoniazid

In 32 patients there were no significant changes in serial chest x rays except those caused by surgical procedures 2 showed marked improvement 11 progression 4 increase in cavity size 4 transient infiltrates 2 new persistent densities and 1 interlobar effusion Catalase tests revealed 25 patients with only catalase negative and 17 with catalase positive resistant organisms 2 first had only catalase negative isoniazid resistant cultures and special mixed cultures later

All except nine patients two of them obese either gained weight slowly or maintained previous weight There was no relation between extent of disease and sedimentation rates Several patients had clinical symptoms or signs of toxicity that could be explained only by persistent multiplication of tubercle bacilli in open cavities with absorption of metabolic products Surgery was performed on 15 patients but failed to cause significant decrease of isoniazid resistant tubercle bacilli in the sputum

The authors suggest that isoniazid inhibits the multiplication of drug susceptible organisms and probably under certain circumstances sterilizes them This direct antimicrobial activity may fail only when the parasite suffers genetic loss of a physiologic function essential for its full pathogenicity If administration is continued the drug may attack not only natively susceptible parasites which may multiply after long periods of metabolic quiescence in necrotic lesions but any drug susceptible reverse mutants making their appearance from drug resistant bacilli

A slight degree of attenuation of tubercle bacilli may manifest itself in a highly significant manner clinically in the partially immune tuberculous patient Apparently the 17 patients who excreted large numbers of isoniazid resistant catalase positive bacilli fared no less well than the 25 who excreted only catalase negative organisms Yet a dead tubercle bacillus will probably always be preferred to a living one however highly attenuated

Course of Pulmonary Tuberculosis during Long Term Single Drug (Isoniazid) Therapy was studied by Kurt

tums of patients with resistant organisms usually also contain varying proportions of susceptible tubercle bacilli the authors attempted to determine the role of the resistant organism (1) when mixed with virulent tubercle bacilli and inoculated into normal guinea pigs and mice and (2) when injected into guinea pigs previously inoculated with virulent tubercle bacilli

In the first experiment all guinea pigs became tuberculin positive The tuberculous lesions consisted of only isoniazid sensitive tubercle bacilli with no resistant organisms In mice some resistant organisms took part in the formation of tuberculous lesions though the sensitive organisms were by far predominant In the second experiment no resistant organisms were isolated from tuberculous lesions of the autopsied guinea pigs All normal guinea pigs became tuberculin positive after injection of the resistant organisms

With regard to the human host it is possible that isoniazid resistant tubercle bacilli play no part in maintenance and spread of tubercular lesions If that is true the bacteriologic relationship to nonimproving patients should be a consistent increase in or at least maintenance of the isoniazid sensitive organisms even when isoniazid resistant organisms are being produced In other words the sensitive organisms are producing the lesions and these organisms are not eliminated by the drug They multiply as sensitive organisms and maintain the active disease and at the same time resistant organisms are produced which play no part in the formation of new lesions

Observations on Pathogenicity of Isoniazid Resistant Mutants of Tubercle Bacilli for Tuberculous Patients R Oestreicher S H Dressler W F Russell Jr J B Grow and G Middlebrook[1] (Denver) studied 45 patients with advanced pulmonary tuberculosis who persistently excreted isoniazid resistant mutants but were maintained on chemotherapy with isoniazid alone for 6-25 months after preliminary combined drug therapy Experiments have revealed that the mutants are strictly limited in ability to multiply in previously uninvolved parenchyma of guinea pig lungs Thus it seemed that any attenuation of isoniazid resistant mutants for human beings should manifest

(1) Am R v T be c 71 (pt 1) 390-405 Ma h 1955

therapy irrespective of the status of the tuberculous lesion or the particular drugs concerned

Studies on Use of High Dose of Isoniazid I Toxicity Studies J Park Biehl and Herman J Nimitz[3] (Cincinnati) state that an outstanding property of isoniazid is its virtual lack of significant toxicity when used in conventional doses Side effects have been a minor part of most clinical reports Except for idiosyncrasies or allergies reactions appear to be transient Statistical analysis of toxicity is difficult because of the nature of the effects and the varied approaches of observers Recorded effects include restlessness insomnia muscle twitching headache vertigo constipation urinary retention and subtle changes in behavior Psychosis and convulsions are more significant phenomena Electroencephalographic abnormalities have been induced by isoniazid in higher doses and fatal status epilepticus occurred in one patient who received 3 mg /kg isoniazid daily and had had epilepsy

The authors studied the toxic effects of isoniazid using doses in excess of 5 mg /kg /day in 116 patients with pulmonary tuberculosis Consistent toxicity was not found ide effects were peripheral neuritis and gastric intolerance Peripheral neuritis was increasingly common with increasing dosage up to 24 mg /kg /day developing in 44% of those given 16-24 mg The neuritis may be due to pyridoxine deficiency which may appear with isoniazid treatment Neuritis identical to isoniazid neuritis may be seen in human pyridoxine deficiency induced by desoxypyridoxine a metabolic antagonist of pyridoxine

Three patients died during the study one possibly of toxic encephalopathy due to isoniazid Another died suddenly of an unknown cause but high dose isoniazid therapy was not blamed The third death was clearly unrelated to the isoniazid Gastric intolerance was seen in 10% most occurred in those receiving 20 mg /kg /day No significant toxic effects on peripheral blood kidneys or liver were noted

Psychiatric and Neurologic Side Effects of Isoniazid and Iproniazid its isopropyl derivative are quite variable in the experience of Hyman Pleasure[4] (West Brentwood

(3) Am R T b 70 430 441 S pt mb 19 4
(4) A M A A h N L & P y h t 72 313 3 0 S pt mbe 19 4

Deuschle Louise Ormond DuMont Elmendorf Jr Carl Muschenheim and Walsh McDermott[2] (New York Hosp Cornell Med Center) Isoniazid has been shown to exert impressive antituberculous activity in pulmonary miliary and meningeal tuberculosis However, isoniazid resistant tubercle bacilli can be isolated from tuberculous patients whether or not they have been treated with the drug The degree of antimicrobial activity of isoniazid compared with other antituberculous drugs and the period during which isoniazid remains effective in a patient are still to be determined

Studies on the first question revealed that at least during the early stages of drug administration the antituberculous activity of isoniazid was equal to that of streptomycin and para aminosalicylic acid (PAS) In miliary tuberculosis and mouse population studies which permitted the most satisfactory quantitative comparisons isoniazid was clearly superior to streptomycin or to streptomycin PAS

To determine if isoniazid usually had only short term usefulness 47 patients with moderately or far advanced pulmonary tuberculosis were started on isoniazid therapy to be continued for at least one year Any patient whose therapy was altered in any way during the year either by a change in drugs or by use of collapse or excisional therapy was eliminated from the study

Thirty two patients completed a year of therapy At some time during the year 29 of the 47 patients were classified as having substantial roentgen improvement and 6 were roentgenographically worse In none did the roentgenographic worsening represent a major spread of the disease Cavity closure (all cavities in each patient) occurred in 15 of 44 with cavitary disease without collapse or excisional therapy At the end of the therapeutic year tubercle bacilli could be cultured from approximately a fourth of the original 47 patients

These observations on the use of isoniazid alone have significance with respect both to choice of chemotherapy of the hospitalized tuberculous patient and to maximal usefulness of home care programs for tuberculosis Reappraisal should be made of the current practice of multiple drug

(2) Am Rev Tuberc 70 228 257 August, 1954

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(3) Am R Tub 70 430 441 S pt mb 19 4
(4) A M A A b N 1 & P y h t 7 313 3 0 pt mb 19 4

N Y) The toxic symptoms are proportional to the plasma level, and the therapeutic effect does not increase when the dosage is raised above 3-4 mg/kg/day Practically all psychotic reactions have occurred in patients receiving more than 8 mg/kg isoniazid daily and in those treated with iproniazid The latter drug produces many more mental symptoms than isoniazid and is no longer used by most physicians In two years at Pilgrim State Hospital Pleasure encountered 16 patients in whom isoniazid apparently produced a toxic psychosis sufficient to cause commitment and 9 patients with psychosis due to iproniazid Euphoria with isoniazid therapy appears due to relief from symptoms of tuberculosis as it is rare in nontuberculous patients Occasionally restlessness increased tension and agitation are seen and can be managed with phenobarbital or by withdrawing isoniazid

In the two year period 602 tuberculous mentally ill patients were treated with isoniazid Nineteen with essential epilepsy were placed on isoniazid after the best dosage of the usual anticonvulsant drugs was determined The number of seizures was not affected Six patients with post traumatic epilepsy were not adversely affected by isoniazid once anticonvulsant therapy was adjusted Four alcoholic patients with rum fits had no attacks on isoniazid without antiepileptic drugs Three of four patients with seizures following prefrontal lobotomy had no additional seizures when isoniazid was given with anticonvulsant medication The fourth had a seizure and looked so ill that isoniazid was discontinued He immediately improved and had no seizures Two postlobotomy patients had no seizures until isoniazid was started the seizures which resulted were readily controlled with antiepileptic drugs although isoniazid was continued Isoniazid without streptomycin was given in 5 mg doses/kg/day to 20 postlobotomy schizophrenics and in 10 mg doses to 5 similar patients One patient had seizures which were controlled with dilantin* and phenobarbital One patient on the 10 mg and two on the 5 mg dosage became agitated until isoniazid was stopped One of five patients with tuberculous meningitis treated with isoniazid had convulsions and died she was moribund when treated and was given 10 mg/kg for one day and half this

dose for two days before the seizures began Isoniazid had no effect on patients being treated with electric shock

Of the 602 patients treated with isoniazid only 3 had to stop taking the drug because of seizures and 2 because of peripheral neuropathy manifested by subjective numbness burning and tingling of the hands and feet Many alcoholics with peripheral neuritis were treated with isoniazid without aggravation of their symptoms The drug does not appear to be dangerous to aged arteriosclerotic or alcoholic patients Since some symptoms may appear early and disappear when the drug is continued while others may appear only after prolonged administration single large doses do not give a reliable test of long term toxicity

Antithyroid Action of Para Aminosalicylic Acid Alastair G Macgregor and Alan R Somner[5] (Edinburgh) confirmed the fact that para aminosalicylic acid (PAS) when used in normal dosage in treatment of tuberculosis in man can produce clinical hypothyroidism Of 83 tuberculous patients treated with PAS for five months or more



F g 45 —S n f m tby d gl d f p t t wh h d ec d PAS h w g hyp pl d d sq mat on f p h l m b f ll d sc la ty d fi fib ×70 (C rt y f M g g A G d S mn A R La et 2 931 936 N 6 1954)

(5) La t 2 931 936 N 6 1954

20 (23%) developed a goiter often with hypothyroidism Studies with radioactive iodine showed changes in thyroid function in all the patients tested while receiving PAS Many had a hypothyroid pattern of radioiodine excretion and in all but one avidity of the thyroid gland for radio iodine was observed on withdrawal of the drug Previously untreated patients showed a depression of thyroid function under treatment with PAS

Although the goitrous and hypothyroid state induced by PAS is usually quickly reversible on withdrawal of the drug it is felt that thyroxin should be given to all patients in whom a goiter is noted or to whom PAS is to be given for more than six months

The following case illustrates the severe changes which may develop

Man 38 died of cor pulmonale six months after hypothyroidism had been diagnosed. He had received 10 6 kg PAS in 79 weeks The thyroid was slightly enlarged There was no nodularity On section it was difficult to make out acinar structure and very little colloid was seen There was an increa e in fibrous tissue and in vascularity Microscopically the gland bore little resemblance to thyroid tissue (Fig 45) The acini were greatly distorted and in many the epithelium had been desquamated

[The very high incidence noted in Edinburgh of damaging effects on the thyroid induced by PAS is in marked contrast to the recorded experience in the United States Here only a few cases have been reported The difference is probably attributable to the lower customary dosage of PAS in this country but possibly more cases are unrecognized than is appreciated —Ed]

Ambulation of Patients with Pulmonary Tuberculosis under Protection of Chemotherapy Preliminary Report is presented by Sidney H Dressler Eleanor M Anthony William F Russell Jr John B Grow John Denst Maurice L Cohn and Gardner Middlebrook[6] (Denver) on 96 patients with advanced active pulmonary tuberculosis Ambulation was started after about 6 weeks of chemotherapy with isoniazid or isoniazid streptomycin and observations were continued an average of 10 months In controlling the acutely active disease and its clinical toxicity isoniazid alone or with other drugs was more dramatically and consistently effective than rest in any form Its principal activity is probably due to its direct antimicrobial action

(6) Am Rev Tuber 70 1030 1041 Dec mbe 1954

the interruption of multiplication of the parasites Treatment in a hospital without long term bed rest had no deleterious effect on the tuberculous infection

Isoniazid therapy may lead to mutants of tubercle bacilli resistant to its action Since many patients still discharging isoniazid resistant tubercle bacilli showed general clinical improvement and new lesions rarely developed in other parts of the respiratory tract or body it is assumed that isoniazid resistance may not have the same alarming significance as resistance to streptomycin or to PAS

Neither isoniazid or other antibiotics nor bed rest eliminates tubercle bacilli still viable but metabolically dormant in closed necrotic lesions Such foci might open after hospitalization causing reactivation Thus they should be given every opportunity to open under protection of chemotherapy with isoniazid in the hope that the initially minimal population of viable bacilli which starts to multiply when such foci ulcerate would soon be sterilized in toto by the isoniazid In other words use of isoniazid alone or with other sterilizing drugs to decrease incidence of tuberculous relapse would require intentional abandonment of long term physical rest

Oral Antimicrobial Therapy of Nonhospitalized Tuberculous Patients is discussed by Arthur B Robins Hans Abeles Aaron D Chaves Morton H Aronsohn Joseph Breuer and Daniel Widelock[7] (Department of Health New York) Daily doses of 300 mg isoniazid and 12 Gm para aminosalicylic acid (PAS) were given orally to 348 ambulatory patients with active pulmonary tuberculosis Known duration of disease was a minimum of five years in at least one third of the patients Many had been treated in a tuberculosis hospital on one or more occasions

X ray signs improved in 39% and sputum conversion occurred in 52% after six months treatment A significant correlation between favorable roentgenographic and bacteriologic response was found Appearance of strains of tubercle bacilli resistant to 1 μg isoniazid/ml was noted in only 8 5% of 82 patients studied Isoniazid PAS is the regimen of choice for nonhospitalized tuberculous patients and the authors suggest that such patients not previously

(7) Am R T be 70 104 105 D mb 1954

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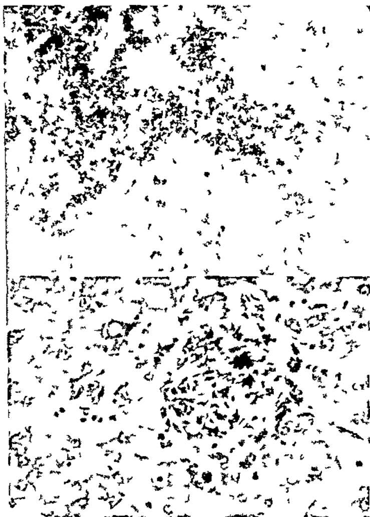
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(6) Am R T be c 70 1030 1041 Dec mbe 1954



F g 46 (t p) —Spl h w g m f t b l ba ll d l g ly t t t om w th t po Z hl N l t × 00

F g 47 (bott m) —L r h w g m ll f w th t b l b ll b ll j l t t p h m l ll Z hl N l ×400

(C t y f O B J R J Cl P th 7 16 5 A g t 19 4)

given drugs should receive this therapy as part of an integrated public health program for management of tuberculosis before during and after hospitalization

[In evaluating this study it should be appreciated that the patients were mostly in the older age group (over 45 years) and that in a substantial proportion the known duration of disease was several years (five years or more in one third of the group) It should be further noted that the patients admitted to the study were in three principal categories (1) they were awaiting hospitalization (2) they refused hospitalization or (3) they had previously been hospitalized on one or more occasions and had left most commonly against medical advice Considering these circumstances and the fact that the patients were fully ambulatory during the entire period of treatment the results are impressive The critics of this program and others of its type fail to appreciate that if it were not provided most of these patients would be receiving no treatment —Ed]

Nonreactive Tuberculosis is defined by J R O Brien[8] as a histologic condition in which there are miliary areas of necrosis containing large numbers of tubercle bacilli surrounded by normal parenchymal cells or a minimal degree of the usual tissue response There are 66 acceptable reports of this condition in the literature In these the course commonly was that of an acute overwhelming infection less often the syndrome presented as a chronic pyrexia of unknown origin sometimes as an obscure anemia or apparently as panmyelophthisis or primary agranulocytosis Skin sensitivity to tuberculin investigated only three times was weakly positive twice and negative once Postmortem examination in 27 cases showed yellow areas of necrosis from pinhead size to 1 cm diameter The spleen was almost always enlarged the liver often No case of tuberculous meningitis has been reported Histologic changes were always found in liver and spleen and almost always in bone marrow Of 14 cases in which the type of tubercle bacillus was identified it was of human type in 10 and bovine in 4

O Brien reports eight new cases which are well represented by the following two

Case 2—Woman 59 began to lose weight 11 months before death Pallor fever and an enlarged spleen were noted after eight months Hemoglobin was then 58% White cell count varied between 1 000 and 2,500 and differential count was normal Sternal punctures showed marked hypocellularity with normal red and white cell maturation

Histologically the liver and spleen showed vast numbers of tubercle bacilli matted into clumps but the surrounding architecture

(8) J Cl Path 7 216-225 A gu t 1954

was not disorganized (Figs 46 and 47) Absence of inflammatory response or fibrosis was remarkable in both organs

CASE 3—Man 25 had chest pain night sweats and productive cough. He became increasingly ill breathless and febrile Tubercle bacilli were found in the sputum only a few days before death Sternal puncture revealed leukemoid reaction

Numerous miliary tubercles were found in the liver spleen and lungs the lungs also showed caseous bronchopneumonia Figures 48 and 49 show that the tissue reaction approached to a slight degree that found normally

It is suggested that in human nonreactive tuberculosis it is the rate of liberation or the quantity of the products of metabolism of the tubercle bacillus that evokes a state of abnormal sensitivity in the patient Alternatively or additionally it is suggested that these people are in an abnormal state and cannot produce a normal sensitivity response

In some patients given cortisone an unsuspected tuberculous lesion may advance rapidly The histology of these lesions is strikingly similar to that found in nonreactive tuberculosis Also the hi tologic picture of lesions in transplacentally infected human babies is often similar to that in nonreactive tuberculosis

It is further suggested that in nonreactive tuberculosis the marrow cells are also in a state of abnormal sensitivity which would explain the coincidence of nonreactive tissue response and the abnormal blood picture

Diaphragmatic Pneumocele Complicating Therapeutic Pneumoperitoneum Review and Report of Four Cases Robert L Guillaudeu and Donald B Stewart[9] (Fitzsimons Army Hosp Denver) designate an air filled ac arising from the diaphragm as a diaphragmatic pneumocele This is not called herniation of the peritoneal membrane because it seems to be a defect in the peritoneal membrane rather than true herniation It is believed that a small tear in the peritoneal membrane over the diaphragm allows air to rise between muscle fibers Possibly at first the wall of the sac is composed of fibrous and areolar tissue with an upper covering of pleural mesothelium Later the upper surface is rubbed by the lower surface of the lung and becomes covered by granulation tissue

Roentgen findings are characteristic but not pathogno

(9) Am R T be 69 74 758 M y 1954



Fig 48 (t ;) —I l t e e po con t of occa al g nt ll and som lymphocyt La g mbe f l f agm t a p ens H m t xyl eo n × 00

F g 49 (bottom) —Lu g h w ng cr t c area w th m mal lymphocyt e f fi g a d some n le d b o ly H m to yl eo × 200

(C t y (U B en J R J Cl l th 16 5 A gu t 1954)

from which the film is taken it cannot be separated from the diaphragm Finally diagnostic or spontaneous pneumothorax will with separation of the lung from the diaphragm confirm the origin of the pneumocele

A diaphragmatic pneumocele is believed to be a contraindication to continuing pneumoperitoneum therapy as in four known cases this was followed by rupture of the diaphragm

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MISCELLANEOUS

Long Term Oxytetracycline (Terramycin®) Therapy in Advanced Chronic Respiratory Infections W H Helm J Robert May and J I Livingstone[1] (London) treated 38 patients with advanced chronic respiratory infections with oxytetracycline The dosage scheme was modified as the series progressed but all patients started on at least 2 Gm daily until the infection had been apparently eliminated or suppressed when the dose was reduced to a maintenance level of 1 1 5 Gm /day Later the initial dose was increased to 3 Gm daily

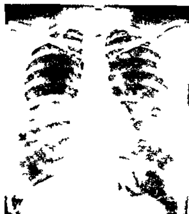
Twenty four patients responded well immediately whereas 14 did not Fourteen with good response had remained on treatment from 6 to 30 months

Long term antibiotic treatment is valuable in some cases of advanced chronic respiratory infection but reinfection is almost certain when treatment is stopped It remains to be seen in what proportion of cases if any treatment can be continued indefinitely without serious toxic effects development of bacterial resistance or overgrowth of fungi or other secondary organisms and whether improvement will be maintained when treatment is ultimately stopped after a long period At present this form of treatment should probably be undertaken only when close clinical and bacteriologic control is possible and should be restricted to advanced cases

Spontaneous Irruption of Air from Lung I Pneumomediastinum Among 60 cases of spontaneous irruption of gas from the alveolus observed by John S Chapman (South

(1) La t 2 630 633 S t 5 1954
( ) Am J M d 18 547 556 Ap 1 1955

monic of diaphragmatic pneumocele The lesion first appears during therapeutic pneumoperitoneum as a small area of radiolucency with a complete surrounding ring (annular shadow) projected below the diaphragm (Figs 50 and







F g 50 (bo l ft) Ch t film h w g l h d w p ject d be l w d ph agm th gh 6th a d 7th a t b

F g 51 (bo)—D t l of n la had w

F g 52 (l ft)—Lat al v w bow g C h p d h d w a g f om p t p rt n f ght d ph gm

(C rt y f Gu ll de R L a d St w t D B Am R T berc 69 745 758 M y 1954)

51) In five to six months it enlarges slowly possibly reaching 5 cm diameter With increase in size most lesions develop apparent trabeculation The size may vary with differences of pleural and abdominal pressures although the general trend is constant slow enlargement On a lateral film the pneumocele is seen to arise from the posterior curve of the diaphragm (Fig 52) Regardless of the angle

tinum seem indicated (1) The development of subcutaneous emphysema about the neck is certain evidence of pneumomediastinum if there is no source of air leak in the neck itself (2) Roentgen demonstration of gas within the borders of the mediastinum may be taken as certain evidence but a para or precardiac (lateral view) lucency alone is not sufficient Such signs call for exclusion of left pneumothorax (3) Detection of a crunch is not sufficient evidence for a diagnosis of pneumomediastinum unless examination excludes pneumothorax or other conditions which might produce the sound (4) In the presence of pneumothorax (usually left) a reliable diagnosis can be made only on the first two points (5) Diminution or disappearance of cardiac dulness with or without crunch calls for exclusion of pneumothorax localized or generalized emphysema or an abnormally high left diaphragm with overlapping gastric or pneumoperitoneal tympany

[The crunching crackling and clicking sounds near the heart which have come to be known as Hammon s sign of mediastinal emphysema are as Dr Chapman points out (I believe correctly) by no means pathognomonic of this condition. My own experience is in agreement that these sounds are more commonly produced by left pneumothorax whether or not there is a sociated pneumomediastinum The necessity for carrying out special roentgenologic maneuvers such as the taking of films in various position at expiration to demonstrate a small spontaneous pneumothorax is pointed out in this excellent study and review of a condition about which there have long been mi conceptions —Ed]

Bronchial Pulmonary Vascular Shunts in Chronic Pulmonary Affections J G Roosenburg and H Deenstra[3] (Utrecht) used cardiac catheterization to demonstrate a pathologic connection of the systemic with the pulmonary circulation in chronic pulmonary diseases The cardiac catheter was maneuvered via the basilic or saphenous vein into the pulmonary artery of the diseased part of the lung Blood samples were taken at various places and the pressure and oxygen saturation of the arterial blood measured

Oxygen saturation of the blood in pulmonary arteries of lungs or lobes showing extensive changes due to tuberculosis or bronchiectasis was found to be equal to that in the systemic circulation or in any case definitely higher than the oxygen saturation of the mixed venous blood This blood can only originate from dilated bronchial arter

(3) D *Chest 26 664 671 December 1954*

western Med School) and his associates there were 10 in which peculiar adventitious sounds near the heart, sounds described as crunching crackling or clicking were noted by more than one observer Each of the 10 was associated with left sided spontaneous pneumothorax All observers agreed that the sound was that known as Hamman s sign of mediastinal emphysema yet there was not a single case of associated subcutaneous emphysema nor acceptable x ray evidence of pneumomediastinum Of the conditions that may be associated with cardiac crunch the commonest is left sided pneumothorax It has also been described in induced pneumothoraxes (explained on the basis of a forcible separation of the pleurae by an air bubble moving back and forth by cardiac activity) in marked bullous emphysema pneumoperitoneum dilated lower esophagus or stomach and pneumomediastinum

Macklin demonstrated that in pneumomediastinum the air follows the vessels In dissecting along vessels air would enter behind the pretracheal fascia at a level above the heart In perforations of the bronchi trachea and esophagus the gas enters posterior to the middle layer of cervical fascia and unless the volume of gas is quite large or the pressure very great air shadows should not be seen anterior to the heart shadow or lateral to the left heart border Reviews of reported cases of spontaneous pneumomediastinum indicate that there is discernible subcutaneous emphysema in only about 25% However it was present in all but one reported fatal case In severe cases when the mediastinum is under great pressure several mechanisms operate Respiratory motion is painful the lungs are displaced and their motion hindered by adjacent swelling of the mediastinum return blood flow through the venae cavae may be impeded and possibly some of the vagal reflexes become operative To possible elements of neurogenic shock may be added failure of the thoracic suction pump If hypoxia develops with pulmonary arteriolar constriction the circulation is likely to fail If there is also spontaneous pneumothorax the series of events would be accelerated

Because of the possibility of confusion of physical and x ray signs certain criteria for diagnosis of pneumomedias

both clinical and bacteriologic but some cases may be due to disturbance of bacterial homeostasis by the common use of such antibiotics as penicillin with resultant super infection by K pneumoniae

The present series of cases is similar to others reported in the literature in the tendency to chronicity of disease with delayed resolution residual cavitation and fibrosis leukopenia and a predilection for middle aged men The clinical picture is variable but many typical cases are asso ciated with organisms of types other than A and B

Klebsiella pulmonary disease may be likened to tubercu losis in that it is resistant to therapy and tends to produce necrosis (especially in Negroes) and fibrosis Resistance to therapy may be due to the presence of conditions un favorable for phagocytic activity including low oxygen tension in necrotic tissue and destruction of alveolar walls which ordinarily provide a surface on which phagocytes can migrate In vitro studies suggest that the best thera peutic agent may be a combination of chlortetracycline oxytetracycline and chloramphenicol

The diagnosis of Klebsiella pulmonary disease is a diffi cult one which requires further clinical and bacteriologic clarification

Pulmonary Aspects of Polyarteritis (Periarteritis) Nodosa are discussed by Howard P Doub Ben E Goodrich and James R Gi h[5] (Henry Ford Hosp Detroit) The general impression is that lung changes in polyarteritis nodosa are not characteristic of the disease however some changes when combined with the clinical picture are highly sug gestive

Of eight patients in whom pulmonary lesions were found at autopsy six had x ray evidence of lung involvement Analysis of the roentgen changes disclosed parenchymat ous infiltration in all Two had moderately pronounced nodulation

In all of the 10 cases not confirmed by autopsy positive biopsy evidence was obtained Two died of clinically active polyarteritis nodosa but roentgen studies disclosed no le sions Three patients had increased vascular markings with suggestive areas of nodulation The rest showed no signifi cant evidence of involvement

(5) Am J Roentg 1 71 85 793 M 1954

ies which have formed wide anastomoses with the pulmonary arteries

Pressure in the pulmonary arteries of affected lungs was not higher than that in normal lungs This is explained by the enormous adaptability of the pulmonary vascular system in which the pressure does not rise until the blood supply is increased more than threefold

It is assumed that in various pulmonary processes the pulmonary artery is first thrombosed that this causes a great increase in caliber of the bronchial arteries and their anastomoses which probably do not function in normal cases and that the pulmonary artery is then recanalized In these pulmonary processes there is a markedly increased blood supply from the bronchial arteries via the anastomoses to the pulmonary arteries The oxygenated blood from the systemic circulation flows partially via the normal route to the bronchial veins which drain into the pulmonary veins and partially through the pulmonary capillaries to the pulmonary veins and thus arrives in the left heart again This means in fact a left right shunt

Pulmonary hemorrhages in chronic pulmonary diseases probably originate in the dilated bronchial arterial system where pressure is higher than in the pulmonary arterial system

[Bronchial pulmonary artery shunts in chronic pulmonary disease have been demonstrated histologically by Liebow and others and a considerable amount of experimental work on this problem has been carried out Few if any clinical studies have been performed heretofore however to confirm the hypotheses based on the pathologic and experimental observations This study shows that left right shunts are indeed common and that relief of the resulting left heart strain is one of the purposes which may be accomplished by pulmonary resection —Ed]

Klebsiella Pulmonary Disease is discussed by William Weiss George M Eisenberg John D Alexander Jr, and Harrison F Flippin[4] A high incidence of pulmonary disease associated with Klebsiella pneumoniae in the sputum is reported for the winter of 1952 53 at the Philadelphia General Hospital Klebsiella pulmonary disease has been recognized more and more frequently in the past decade and it is suggested that many cases of so called nonspecific lung abscess may be due to this organism The reason for the increased incidence may be improved case finding

(4) Am J M Sc 2 8 148 155 Aug 1 1953

in the central portions of the lung and do not extend to the periphery

Diffuse Interstitial Fibrosis of Lungs has been believed to begin insidiously as a widespread inflammation involving all lobes of both lungs diffusely with albuminous fluid containing few polymorphonuclear leukocytes and a small amount of fibrin filling the alveoli Soon marked proliferation of connective tissue occurs thickening the alveolar walls and obliterating many of the air sacs As the fibrosis increases and spreads pressure in the pulmonary artery increases leading to cardiac failure It has been suggested that either a virus or a chemical agent might be the cause

In a number of reported cases hexamethonium and hydralazine (apresoline®) hydrochloride have led to fatal interstitial pneumonia identical with acute interstitial fibrosis of the lungs In two the lung lesion was an organized fibrinous pulmonary edema attributed to attacks of left heart failure probably modified by intermittent lowering of blood pressure by hexamethonium

If the process represents a series of attacks of interstitial pneumonitis each followed by inflammatory fibrosis Charles Pokorny and C A Hellwig[6] (Halstead Kan) question why the inflammatory fibrinous exudate in the alveolar septa is not resorbed but becomes organized Carnification of the lung after lobar pneumonia has much in common with diffuse interstitial fibrosis in that the alveolar walls become thicker and fibrous Why in rare cases of lobar pneumonia resolution and resorption of exudate fail to occur has not been explained Buechner has stated that the fibrin of inflammatory exudate must be liquefied to become resorbed if it becomes hyalinized fibroblasts invade the fibrinous masses and organize it by collagenous fibers During the resolution of pneumonic exudate the lung contains an unusual amount of fibrinolytic enzyme It seems probable that fibrinolysin in plasma or lung tissue is liberated by inactivation of antiplasmin Fibrinolysis is apparently a complex enzymatic process involving at least four chemical substances Blocking between two links of the chain will prevent fibrinolysis and proliferation of fibroblasts will result The resolution of fibrinous inflamma

(6) A M A A h P th 59 38 387 M h 1955

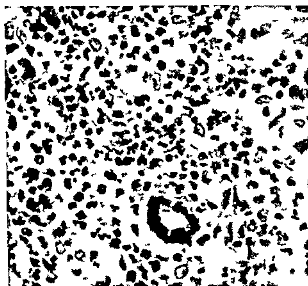
The lung changes roughly followed the pattern described by earlier writers There was moderate or pronounced hilar enlargement in most cases The milder changes were prominence of the linear markings throughout the lungs with an occasional small localized density difficult to classify



F g 53 —Typ l batw ng haped a a of filt t on n both lu g (C u-t y of Doub H P et / Am J Roentgen l 71 785 793 M y 1954)

More advanced changes consisted of extensive areas of perivascular and parenchymal infiltration with some generalized haziness extending from the hilar areas into the lung fields The areas of involvement were not selective and occurred in the upper lung fields almost as frequently as in the bases Several showed the typical batwing shaped areas of infiltration (Fig 53) spreading from the hilar areas with other areas of the lungs relatively clear These areas often cleared considerably but later more pronounced changes developed which persisted until death The areas were similar to those in chronic uremia which are typically

with lipid material Aggregation of the xanthomatous tissue formed discrete tubercles Some cysts were lined with lipid filled giant cells (Figs 54 and 55) Weigert s stain demonstrated destruction of the elastica in alveolar and atrial walls where histiocytic infiltration had occurred



F g 55—X th m t m wb h d t ety f ll f d h g t ll d l b h t oc t nd ell d ph l H m t xyl n eo 150 (C rt y f M Don ld A M a d Sh k R A A h D Ch ldh d 9 1 131 Ap l 1954)

Study of liver tissue in five cases revealed xanthomatous infiltration in four

Dyspnea and honeycomb lung in children are probably due to generalized xanthomatosis Tuberous sclerosis the other possible cause is even rarer than pulmonary xanthomatosis Diagnosis can be made from biopsy of a lymph node However since the clinical course of xanthomatosis leads to early death diagnosis can be confirmed at autopsy

Histiocytic Reticulosis and Honeycomb Lungs N G B McLetchie and D P Reynolds[8] (Dalhousie Univ) state that histiocytic reticulosis embraces three syndromes of

(8) C d M A J 71 44 49 July 1954

tory exudate and formation of granulation tissue according to Selye are under hormonal control In animal experiments cortisone and corticotropin can prevent fibroplasia *whereas other hormones will stimulate it In this* connection it is interesting to note that hexamethonium may produce pulmonary fibrosis

Honeycomb Lung and Xanthomatosis A M MacDonald and Robert A Shanks[7] (Univ of Glasgow) present seven



F g 54—Ph t m c og aph of cy t d l g f t l d giant c lls n the w ll Xa th m t t s p t dj t to th y t w th nt ll la fat pp g d k Sud n III d IV ×45 (Cou t y of M cD ald A M a d Sh k R A Arch D s Ch ldhood 29 1 7 131 Ap l 1954)

cases of honeycomb lung with generalized xanthomatosis

Pathologic findings were similar in all seven cases Grossly the lungs were voluminous and mottled with pale solid areas alternating with translucent cystic areas under smooth pleura On section the cysts had a honeycomb appearance and mean diameter of 0 25 cm Histologically the cysts were distentions of alveoli atria and respiratory bronchioles Septa and alveolar walls were irregularly infiltrated by histiocytes which were densely packed polygonal cells with oval or indented nuclei and cytoplasm often filled

(7) A h D s Ch ldhood 29 127 131 Ap l 1954



F g 56—M ph l g pp f h y mb l g (Court y f M Let h
N G B d R y ld D P C d M A J 71 44 49 J ly 1954)

lymph nodes disappeared completely within four weeks There was no clinical enlargement of liver or spleen and blood values were normal There were no bone abnormalities other than the skull lesion This was a firm subcutaneous nodule 2 cm in diameter fixed to the deep structures Headaches increased on pressure X ray examination revealed a small rarefaction of the bone underlying the lesion but no surrounding sclerosis Exploration revealed a firm

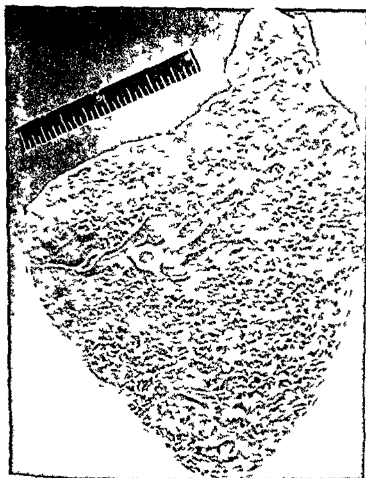
unknown etiology—Hand Schuller Christian and Letterer Siwe disease and eosinophilic granuloma of bone—believed to represent clinical variations of one basic lesion In addition there are cases which are clinically intermediate

Honeycomb lungs are found frequently in histiocytic reticulosis Often the only other manifestation is diabetes insipidus The lungs have the feel of a sponge and a milky fluid can be expressed Photography with strong oblique lighting brings out the texture to advantage (Fig 56) The process involves a generalized expansion of the lymphoreticular apparatus of the lungs with progressive histiocytic differentiation and subsequent fibrosis and lymphedema Fibrosis is coarse around the anatomic lobules With fibrosis spreading from the lymph centers atrophy of some air sacs and general coarse emphysema the spongelike condition develops Generalized reticulation associated with miliary mottling throughout the lung field forms small annular shadows on x rays Apparently the cellular stage can wax and wane and even resolve The use of the terms thin walled or air cysts is unfortunate as the honeycomb appearance is a configuration produced by interstitial histiocytic proliferation and fibrosis its peculiar character determined by localization of the lymphoreticular system of the lungs

Woman 37 10 years earlier had increasing breathlessness for 2 years The tuberculin reaction was negative she had no sputum and tubercle bacilli were never found She was well nourished and looked healthy There was no clinical enlargement of the liver spleen or lymph nodes Radiologic examination revealed heavy mottling throughout both lung fields The mottling frayed out to a reticular arrangement with a distinct honeycomb pattern Because of the negative tuberculin reaction sarcoidosis was the tentative diagnosis

For two years she had swellings of the lymph nodes sometimes tender on both sides of the neck and above the clavicles The glands took about three weeks to swell remained for a similar period and gradually disappeared in about the same length of time

Six weeks before hospitalization she had severe frontal and right sided headaches which came on suddenly and became more frequent then constant She had also noticed a lump on her head which increased in size Apart from breathlessness on exertion present for 10 years and her headaches she had no other complaints and appeared healthy Radiologic examination revealed reticular fibrosis throughout both lungs fields with only a suggestion of honeycomb The density and honeycomb definition was much less marked than eight years before Conspicuous bilateral enlargement of cervical



1 Fg 56—M ph l g pp a f hon mb l g (C t y f M L t h
G B t R yn ld D P C d M A J 71 44 49 J ly 19 4)

lymph nodes di appeared completely within four weeks There was no clinical enlargement of liver or spl en and blood values were normal There were no bone abnormalities other than the skull le sion This was a firm subcutaneous nodule 2 cm in diameter fixed to the deep structures Headaches increased on pressure X ray examination revealed a small rarefaction of the bone underlying the lesion but no surrounding sclerosis Exploration revealed a firm

white tumor involving the whole thickness of the calvarium and attached to the underlying dura Examination of the nodule revealed the classic picture of eosinophilic granuloma

This case presents unusual features The chronicity is not unique but the possibility of long standing and station ary pulmonary disease is not generally appreciated Al though bone lesions may regress permanently and lymph node lesions temporarily recurrent lymphadenopathy is unique in the literature Without biopsy of the skull lesion the diagnosis would have remained obscure

Pulmonary Tuberous Sclerosis and Its Relationship to Other Forms of the Disease are discussed by John Daw

Fig 57—E la ged v w f l g fi ld sh w g er l am ll group of cy t a d g ral d et culat on (Court y f D w on J Quart J M d. 23 113 145 Ap l 1954)

son[9] (London) Tuberous sclerosis was encountered in 72 of 21 579 patients admitted to hospitals for the mentally defective in 21 years (1 in 300 admissions) and it is estimated that incidence is 1 in 150 000 in the general population The abortive forms occur as often as the major disease More female than male patients were found (36 of 64 patients) In records of 25 patients who died and 39 living pulmonary involvement was found once Of seven other patients with adenoma sebaceum and normal mentality one had lung involvement

In addition to these two cases of pulmonary tuberous sclerosis two patients seen because of pulmonary symptoms (pain in the chest and breathlessness) had a clear history and findings of tuberous sclerosis Three of the four were women which is characteristic of the pulmonary complication which has its onset in adult life in contrast to early cutaneous and cerebral features Chronic progressive breathlessness recurrent pneumothorax occasional hemoptysis diffuse miliary or small cystic shadows in the chest x ray (Fig 57) and cough are common Infection is absent or late in development Death usually occurs about five years after onset of pulmonary symptoms and is due to asphyxia from lung destruction spontaneous pneumothorax or right heart failure In two of this series lung biopsy specimens were taken during pleurodesis There was protuse overgrowth of connective tissue smooth muscle and blood vessels leading to the formation of numerous small cysts

Use of Trypsin or Streptokinase Streptodornase for Therapy and Prevention of Atelectasis Sidney Kofman Mark H Lepper George Gee Jackson and Harry F Dowling[1] (Univ of Illinois) report on 24 patients having acute poliomyelitis with pharyngeal and respiratory weakness and requiring tracheotomy and mechanical respiration They were placed by alternation in four groups each of which was given one of the following aerosols (1) polymyxin plus isotonic sodium chloride (nonenzyme controls) (2) trypsin (3) polymyxin plus trypsin and (4) polymyxin plus streptokinase streptodornase No apparent difference was noted in the clinical course of patients in the first

(9) Q rt J M d 3 113 145 Ap 1 1954
(1) Am J M S 228 43 -439 O t b 1954

three groups Three patients experienced severe reaction to aerosol inhalation of the streptococcic enzymes Since *bronchopneumonia developed in one of these patients shortly* after administration of the enzymes streptococcic enzymes are not recommended for this type patient

In 11 patients 21 direct instillations of trypsin into the tracheobronchial tree were given when atelectasis was suspected 9 received 10 direct instillations of isotonic sodium chloride Trypsin appeared beneficial in 42.9% of instillations and similar improvement in the clinical course occurred in 10% who received saline Reactions characterized by transient usually mild increase in respiratory difficulty followed 52.6% of direct instillations of trypsin but were not noted after sodium chloride

Since trypsin appeared effective in 42.9% of the instillations and since half the instillations were likely to have been into the appropriate bronchus the effect seems significant These enzymes are recommended if instillation can be made directly into the bronchus of a known area of bronchial obstruction otherwise risk of adverse reaction is *too great to justify random instillation*

Bronchography with Oily Dionosil a recently developed medium is discussed by Carl P Wisoff and Benjamin Felson (Cincinnati) Since its introduction in 1922 lipiodol® has been generally accepted as the best available contrast medium but it is persistently visible on chest x rays made long after instillation Various rapidly clearing water soluble mediums have been developed but they introduced a new objectionable feature bronchial irritation Dionosil differs from other mediums in that it is a suspension rather than a solution or an iodized oil It is closely related chemically to diodrast®

Experience with 30 bronchograms showed that oily dionosil compares favorably with other contrast mediums It is much less irritating to the tracheobronchial tree than the water soluble mediums In seven cases histologic study revealed no significant inflammatory reaction in the lungs There is no significant difference between dionosil and lipiodol® in contrast density or detail seen in x rays but dionosil and the water soluble mediums are slightly more

(2) J Thoracic Surg 29 435-446 Apr 1955

difficult to see fluoroscopically than lipiodol® The major advantage of dionosil over lipiodol® is its rapid disappearance from the roentgenogram It clears somewhat more slowly than the water soluble mediums This is also an advantage since it is not necessary as with water soluble mediums to hurry the examination in order to avoid the blurring and smudging which obscures the detailed delineation of bronchi The rapid clearing of dionosil virtually complete in 24 hours is in part due to its low viscosity which more readily permits its expectoration and to the speedy absorption and excretion of the iodide There was no evidence of harmful effects

THE BLOOD *and* BLOOD-FORMING ORGANS

WILLIAM B CASTLE, M D

PART III

THE BLOOD AND BLOOD FORMING ORGANS

GENERAL CONSIDERATIONS AND SPECIAL TECHNICS

Number and Distribution of Human Hemic Cells have been calculated by Edwin E Osgood[1] (Univ of Oregon) for standard man (table) values per kilogram may be obtained by dividing the figures by 70 and values for other age and sex groups and species may be calculated by the same principles Results of the calculations at first seem surprising but consideration of their implications explains many perplexing observations Values for the erythrocyte series account for the straight line arithmetical increase and disappearance rate observed when erythrocytic destruction is absent A fundamental conclusion of the study is that leukocytes are not really blood cells i e only a small proportion (1/40 to 1/400) of those outside the hemopoietic organs are present in the blood at any one time Leukocyte values account for the straight line arithmetical decrease and increase after a single massive dose of radiation and for increases and decreases observed in marrow cultures and in patients receiving x radiation There will be logarithmic changes when isotope therapy with a logarithmic decay is used where there are logarithmic effects on cell division The number of neutrophils outside the blood forming organs and blood could easily account for rapid disappearance of these cells in the blood after adrenaline or adrenocortical activity rapid accumulation of hundreds of grams of these cells in pneumonic consolidations peritonitis empyema or abscesses and for inability to raise the leukocyte level by transfusing leukocytes Their rapid disappearance in allergic reaction could also be explained by increased rate of migration from the blood Relatively enormous num

(1) Bl od 9 1141 1154 Dec mb 1954

NUMBER AND DISTRIBUTION OF HUMAN HEMIC CELLS

C ll Series	H mic C lls H ma opoie Orga					H m C ll O id H mat po O g					T t l H Body C	
	M ow			Lymphocy T nd s es		Blood		R tio	Ou id Blood nd Blood f m g O			
	%	N of C ×10	G m	N f C l ×	Gram	N of C l	Gra	m/	N l C ll	G m	N f C ll	(
E yth ocyt e	19	6	100	0	0	27×10	~500		0	0	7 6×10	600
G loc yt e	56	18	300	0	0	90×10	10	1/60	12×10	600	3×10	1600
Lymphocyt e	12 5	4	100	4	100	12×10	3	1/400	3 ×10	1300	6×10	1500
Oth r H m Cells	1 5	4	[illegible]00	4	200	2×10	1	1/400	8×10	400	1 6×10	500
T t l Le kocytes	81	26	1[illegible]00	8	300	34×10	14	1/200	72×10	2300	1×10	3800
Fat Blood C et e T s			1 00		400							
Tot l T ss e	WBC/ mm 1×10		3000		00							

Monocyt pla mocyt e phil b soph l thrombocyt e s and d s nteg ated c lls

bers of eosinophils promptly appearing in any area of aller gic reaction long before an increase in blood eosinophils and rapid disappearance of eosinophils after adrenaline or ad renocortical action could be explained by a simple redis tribution between blood and tissue

Perhaps the most surprising values are those for the lymphocytic series However the frequency with which

small round cell infiltrations are seen about capillaries in tissue sections and the facts that one to eight times the total lymphocytes in the blood stream enter the blood every 24 hours from the thoracic duct alone and that diverting this flow in man has little effect on lymphocyte count make these values seem more reasonable Monocytic histiocytic and plasmacytic series are widespread in body tissues generally particularly in areolar tissue

These observations explain the rapid disappearance of leukocytes from the blood stream after massive transfusions of leukocytes or in parabiosis or cross circulation experiments and make it unnecessary to postulate short life spans which are totally incompatible with desoxyribonucleic acid uptake of P^{3} for these cells These life spans merely represent the mean time in the blood stream on one trip for cells which may enter the blood several times in their true life span The figures given would account for the relatively large numbers lost from the body daily into the gastrointestinal tract Evidence of Bierman *et al* suggests that many leukocytes are in the lungs the largest and only capillary bed through which the entire blood volume passes in any one circulation Thus it is postulated that leukocytes constitute a motile army constantly shifting to sites where they are most needed and that their number varies greatly in different locations according to proportion of total capillary bed open in that area at a particular time Probably great shifts of leukocytes occur in relation to digestion and other visceral activity and in response to inflammation or allergic reaction

The type of cell division described accounts for the marrow appearance usually called maturation arrest on the basis of early cell death a decreased rate of cell division or beginning regeneration after a period of hypoplasia and also for the hiatus leukemicus

✓ **Metabolism of Hemoglobin and of Bile Pigment** is discussed by Irving M London (Columbia Univ) Hemoglobin which has a central role in metabolic processes is composed of a pigment heme or ferrous protoporphyrin and of a protein globin Heme compounds transport and store oxygen make oxygen available to the cell and con

(2) B ll N w York A d M d 30 09 5 5 J ly 1954

tribute to oxidation of cellular constituents—the basic energy yielding reactions of living matter They reflect the development of special function Reversible binding of oxygen and splitting of hydrogen peroxide and its activation are best performed by the heme protein molecule specific for each function Heme can carry out these functions at a lower level *and inorganic iron has a primitive or even lower* functional level The protein moiety markedly enhances and differentiates these functions The protein portion of hemoglobin (globin) is abnormal in some diseases such as sickle cell disease and various hemoglobins whose proteins vary can be distinguished by electrophoresis alkali denaturation solubility properties and chromatography The heme portion of these hemoglobins is normal

Isotopic technics have contributed greatly to elucidation of the mechanism of heme synthesis Glycine is a specific precursor and acetate is utilized via a succinyl intermediate formed from condensation of succinate and glycine Two molecules of the intermediate (delta amino levulinic acid) combine to form a pyrrole with a structure similar to or identical with that of porphobilinogen Evidence indicates that porphobilinogen a monopyrrol is a precursor of protoporphyrin uroporphyrin III and coproporphyrin III which contain four pyrrol nuclei Whether the last two are by products or on the main route of synthesis of protoporphyrin remains to be established

If glycine labeled with N^1 is given to a normal man and hemin subsequently isolated from the peripheral erythrocytes the curve of N^{15} in hemin indicates that the life span of normal erythrocytes is about 120 days and that most of the cell population is destroyed between days 90 and 150 In normal man about 250-300 mg bilirubin should be produced daily principally in reticuloendothelial tissues from degradation of hemoglobin of newly destroyed erythrocytes This bilirubin presumably bound to protein is converted in the liver to unbound form In the intestine bilirubin is reduced to urobilinogens a large portion of which is reabsorbed and re excreted into the intestine Normally urobilinogen is excreted almost completely in feces (to 240 mg daily) and little or none (to 4 mg) in urine

Serum bilirubin can be measured by the van den Bergh

reaction In normal serums and those of many patients with hemolytic jaundice the addition of alcohol is essential for a rapid reaction (indirect) In obstructive jaundice the reaction occurs rapidly without alcohol (direct) Indirect reacting bilirubin is evidently precipitated with the globulin fraction whereas direct reacting bilirubin is precipitated with albumin

In hemolytic processes capacity of the liver to handle bilirubin may be exceeded so that bilirubinemia of indirect reacting type occurs in addition the large amounts of urobilinogen formed and reabsorbed from the intestine may exceed liver capacity for re excretion so that increased urobilinogen appears in the urine Evaluation of gross bile pigment metabolism in a patient must include (1) amount of hemoglobin destroyed daily (2) functional capacity of the liver to excrete bilirubin into bile (3) patency of biliary tree (4) functional capacity of intestinal bacteria to reduce bilirubin to urobilinogens (5) functional capacity of liver to re excrete urobilinogen and (6) threshold of kidney for excretion of direct bilirubin

Investigation of the origins of bile pigment by isolation of hemin from erythrocytes and stercobilin from feces after administration of N^{15} labeled glycine indicates that in a normal man at least 10 15% of bile pigment is derived from one or more sources other than hemoglobin of mature circulating erythrocytes In a patient with untreated pernicious anemia this was increased to 40% and in a patient with congenital porphyria to at least 30% Investigation of the nature of these alternative sources has revealed that hematin and protoporphyrin unbound to globin can be converted to bile pigment in the mammalian organism

[This article and its excellent diagrams deserve study in the original —Ed.]

Use of Radioactive Sodium Chromate to Evaluate Life Span of Red Blood Cell in Health and Certain Hematologic Disorders is reported by Raymond C Read Graham W Wilson and Frank H Gardner[3] (Harvard Med School) When results are plotted on semilogarithmic co ordinates a linear function is obtained Linear loss of Cr^{51} activity is reproducible over the time interval in which 50% of radio

(3) Am J M S 2 8 40 52 July 1954

tribute to oxidation of cellular constituents—the basic energy yielding reactions of living matter They reflect the development of special function Reversible binding of oxygen and splitting of hydrogen peroxide and its activation are best performed by the heme protein molecule specific for each function Heme can carry out these functions at a lower level and inorganic iron has a primitive or even lower functional level The protein moiety markedly enhances and differentiates these functions The protein portion of hemoglobin (globin) is abnormal in some diseases such as sickle cell disease and various hemoglobins whose proteins vary can be distinguished by electrophoresis alkali denaturation solubility properties and chromatography The heme portion of these hemoglobins is normal

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If glycine labeled with N^{15} is given to a normal man and hemin subsequently isolated from the peripheral erythrocytes the curve of N^{15} in hemin indicates that the life span of normal erythrocytes is about 120 days and that most of the cell population is destroyed between days 90 and 150 In normal man about 250 300 mg bilirubin should be produced daily principally in reticuloendothelial tissues from degradation of hemoglobin of newly destroyed erythrocytes This bilirubin presumably bound to protein is converted in the liver to unbound form In the intestine bilirubin is reduced to urobilinogens a large portion of which is reabsorbed and re excreted into the intestine Normally urobilinogen is excreted almost completely in feces (to 240 mg daily) and little or none (to 4 mg) in urine

Serum bilirubin can be measured by the van den Bergh

reaction In normal serums and those of many patients with hemolytic jaundice the addition of alcohol is essential for a rapid reaction (indirect) In obstructive jaundice the reaction occurs rapidly without alcohol (direct) Indirect reacting bilirubin is evidently precipitated with the globulin fraction whereas direct reacting bilirubin is precipitated with albumin

In hemolytic processes capacity of the liver to handle bilirubin may be exceeded so that bilirubinemia of indirect reacting type occurs in addition the large amounts of urobilinogen formed and reabsorbed from the intestine may exceed liver capacity for re excretion so that increased urobilinogen appears in the urine Evaluation of gross bile pigment metabolism in a patient must include (1) amount of hemoglobin destroyed daily (2) functional capacity of the liver to excrete bilirubin into bile (3) patency of biliary tree (4) functional capacity of intestinal bacteria to reduce bilirubin to urobilinogens (5) functional capacity of liver to re excrete urobilinogen and (6) threshold of kidney for excretion of direct bilirubin

Investigation of the origins of bile pigment by isolation of hemin from erythrocytes and stercobilin from feces after administration of N^{15} labeled glycine indicates that in a normal man at least 10 15% of bile pigment is derived from one or more sources other than hemoglobin of mature circulating erythrocytes In a patient with untreated pernicious anemia this was increased to 40% and in a patient with congenital porphyria to at least 30% Investigation of the nature of these alternative sources has revealed that hematin and protoporphyrin unbound to globin can be converted to bile pigment in the mammalian organism

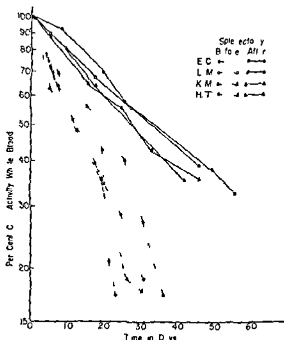
[This arti le and its excellent diagrams deserve study in the orig nal —Ed.]

Use of Radioactive Sodium Chromate to Evaluate Life Span of Red Blood Cell in Health and Certain Hematologic Disorders is reported by Raymond C Read Graham W Wilson and Frank H Gardner[3] (Harvard Med School) When results are plotted on semilogarithmic co ordinates a linear function is obtained Linear loss of Cr^{51} activity is reproducible over the time interval in which 50% of radio

(3) Am J M S 28 40 5 J ly 1954

activity has disappeared hence results are recorded according to half life of tagged cells

Mean half life of Cr^{51} tagged red cells in five healthy males was 26 days (range 23 30 days) In three, survival



F g 58—S l of Cr^{51} t gg d d c lls t g t J h m lyt a em b fore nd ft spl t my Per tag of Cr a t t plott d o emil g r thm o o d n te (C urt y f Read R C *et al* Am J M S 228 40 52 J ly 1954)

studies of chromium tagged red cells and Ashby differential agglutination studies were done simultaneously and a value of 79 days for the half life elution of Cr^{51} was obtained

Red cell survival studies were made in 14 anemic patients Four with congenital hemolytic anemia studied before and 10 days or more after splenectomy exhibited marked increase in disappearance of tagged cells before operation in three mean half life was 11 5 days and in one 19 days (Fig 58) All had normal peripheral blood values after splenec

tomy and the mean half life of tagged erythrocytes was 30 5 days indicating that the red cell survives normally in congenital hemolytic jaundice after splenectomy and that rate of Cr^{51} elution from normal and abnormal red cells is essentially equal

In three patients with myeloid metaplasia Cr^{51} studies indicated that red cells in this disorder (characterized by marked variations in size and shape) as well as normal transfused red cells had a shortened survival period In two of these patients survival of red cells was normal after splenectomy In one with thalassemia minor and splenomegaly moderately increased hemolysis with a Cr [1] half life for red cells of 15 days was observed before splenectomy afterward red cell survival was normal with half life of 25 days Two patients with hypoplastic anemia who required frequent transfusions had normal survival times but a third in whom lymphatic leukemia later developed had short red cell survival Two patients with acquired hemolytic *ic anemia had short half life values of six and seven days* In the latter cortisone increased the value to 10 days In a patient with anemia and uremia the Cr^{51} half life was not definitely short

The Cr^{51} technic requires venous blood for estimation of red cell radioactivity while Ashby studies may be done with capillary samples if necessary Limitation of sample size and radioactivity hazard contraindicate tagging of red cells by this method in infants and small children Conversely the Cr^{51} method has many advantages It evaluates turnover of the patient s own cells and is not limited in application by presence of suitable blood groups Cells are tagged easily with minimal trauma Red cells need not be washed with saline which may distort the results in severe hemolytic disease Use of a closed plastic bag system lessens the chance of contamination and disposability reduces hazards from radioactivity Preliminary phlebotomy is unnecessary since small quantities of blood may be transfused Hazards of blood group sensitization and serum jaundice are also avoided

Use of Cr^{51} and Fe [9] in Combined Procedure to Study Erythrocyte Production and Destruction in Normal Human Subjects and in Patients with Hemolytic or Aplastic Anemia

is discussed by Irwin M Weinstein and Ernest Beutler[4] (Univ of Chicago)

METHODS—*Iron plasma clearance and turnover*—Radioiron (Fe^{59}) obtained as $FeCl_3$ and free from Fe^{55} was adjusted to pH 6 and autoclaved Two to four microcuries of iron was added to 20 ml plasma and incubated at 37 C for 30 minutes Radioactivity was counted and the mixture injected intravenously Hourly or less frequent heparinized blood samples were obtained for four to eight hours and hematocrits determined Plasma iron was determined by counting in a well type scintillator Plasma iron turnover (mg / kg / day) was determined by the formula

$$\frac{0\,693 \times \text{plasma iron mg/ml} \times \text{plasma vol} \times 24}{T\ ½\ \text{in hr} \times \text{weight in kg}}$$

Percent iron utilization—Heparinized whole blood samples were obtained 24 hours after plasma clearance was determined then every other day Hematocrit values were determined and radioiron counts made (Fe^{59}/minute/mm red cells) Washed cells were not neces sary as plasma iron clearance was complete in 24 hours The percent of iron clearance was determined by

$$\frac{\text{counts/min/ml red cells} \times \text{red cell vol} \times 100}{\text{total counts/min injected}}$$

Cr^{51} blood volume and survival time—After labeling the red cells of a sample of patient s blood with Cr^{51} it was reinjected intravenously After a mixing period a blood sample was withdrawn and the formula

$$\frac{\text{counts/min/ml preinjection sample} \times \text{ml blood injected}}{\text{counts/min/ml postinjection sample}}$$

was used to determine the total blood volume Normal value is 50 80 ml /kg The same formula was applied to blood samples drawn on subsequent days as a measure of tagged red cell survival time

Red cell volume was obtained by multiplying the total blood vol ume by the uncorrected hematocrit (normal 23 36 ml /kg) Plasma volume was calculated by subtracting red cell volume from total blood volume (normal 27 44 ml /kg) The Cr^{51} labeled erythrocyte apparent half survival times were calculated without using a cor rection for Cr^{51} elution (normal 33±3 2 days)

With the use of a pulse height selector radioactivity of Fe^{59} could be differentiated from Cr^{51} in the same blood sample as there is marked difference in intensity of the gamma emissions

In six normal subjects maximum Fe utilization account ing for 80 95% of the injected radioiron was within 7 days in two and 12 days in four The half time Fe^{59} plasma clear ance was 1 2 hours The Fe^{59} plasma turnover was 0 38 0 65 mg /kg /day One patient with hemolytic anemia had accelerated maximal utilization in about seven days but of

(4) J Lab & Cl Med 45 616 6 Ap 1 1955

less than 50% of the injected radioiron [This implies preferential reutilization of iron from recently destroyed red cells —Ed] Red cell survival time was decreased and plasma clearance time accelerated Plasma clearance may be so rapid that results based on this measurement may not be quantitatively accurate Results in one case of aplastic anemia showed delayed Fe^{59} plasma clearance poor utilization of iron and a normal survival curve

Evidence of accelerated blood destruction by the Cr^{51} technic indicates therapeutic trial with cortisone and ACTH and possibly splenectomy if there is true blood destruction and not active gastrointestinal bleeding

[In general these result confirm those of others using the technics separately —Ed]

↓ The next five articles selected from among several more are concerned with the regulation of erythropoiesis which as discussed in the first article is now regarded as only *ind rectly* responsive to the circulating hemoglobin concentration Some may hesitate to accept this with finality because there is presently so little agreeme t as to the nature of the erythropoietic humor and none as to its po nt of origin —Ed.

Stimulus for Erythropoiesis Walter S Root[5] (Columbia Univ) reviews the reported experimental evidence pertinent to this problem Changes in concentration and mass of erythrocytes whether due to external loss or introduction of foreign red cells soon disappear and previous levels are restored within days Presumably the organism possesses some mechanism which regulates this balance Miescher suggested that a relative hypoxia is always present in bone marrow and constitutes a stimulus for erythropoiesis insuring a steady supply of red blood cells to replace those destroyed each day At an altitude oxygen tension and arterial blood content would be decreased subjecting bone marrow to greater hypoxia and stimulating erythropoiesis more intensely This explanation has been extended to other types of hypoxia thus anemic hypoxia chronic carbon monoxide inhalation and some secondary anemias are presumed to stimulate bone marrow because of low or defective oxygen capacity Evidence for hypoxic stimulation of bone marrow is indirect and rests on the association of erythroid activity with conditions known to produce hypoxia

In dogs maintained for 100 days at moderate anemic levels Grant found that although as much as 3 2 Gm hemo

(5) J Mt S H p 20 331 338 M Ap 1954

globin daily was formed in some animals there was no significant difference in oxygen saturation of bone marrow blood during the anemic period and before bleeding Studies by Hecht and Samuels indicate that marrow hypoxia is present in patients with reduced arterial oxygen tension or with slowed blood flow However erythropoiesis may be quite intense as in polycythemia vera without any defect in oxygenation of bone marrow blood or unusual degree of unsaturation of bone marrow blood

There is thus no convincing evidence that lowered oxygen tensions exert their effects directly on marrow tissue Presumably hypoxia acts at some other site the bone marrow being activated secondarily The nervous system has been considered particularly by European workers

Schafer induced generalized vasospasm and hypertension *by removal of carotid sinuses and section of depressor* components of vagus nerves Five of 13 dogs were reported to be polycythemic as estimated by red cell volume Sisson Cain and Root however repeating Schafer's experiments found that red cell and plasma volumes immediately after the final operation and for seven months afterward did not differ significantly from control values

Removal of almost any endocrine gland results in anemia usually a reduction of 10 20% of formed elements This can be corrected by injection of an extract of the gland or its active hormone After hypophysectomy the red cell volume of the rat is said to decrease to nearly half the control value Fresh sheep anterior pituitary orally repaired the anemia of such rats and brought the circulating red cell volume to higher than normal levels However hypophysectomy *does not appear to cause any serious defect* in the erythropoietic mechanism for hypophysectomized and normal rats show the same hemopoietic response to a simulated altitude of *22 000 ft*

Carnot and Defiandre found that plasma from slightly anemic rabbits injected into normal rabbits produced a small increase in red cells in the peripheral blood The unknown stimulating substance was called hemopoietine Plasma from severely anemic rabbits *had no effect Single injec*tions of small amounts of plasma presumably containing small amounts of hemopoietine does not yield consistent results

To test the Carnot hypothesis Reissman placed parabiotic rats for several hours a day in a special breathing chamber in which one member breathed a gas mixture containing 8-10% oxygen and the other breathed air Both had a polycythemic response The increase in erythroid elements in the bone marrow of both animals is assumed to mean that an agent capable of stimulating red bone marrow was formed in the hypoxic rat and passed by the circulation to his partner Grant placed lactating rats and mice in a low pressure chamber for six hours a day while their litters remained at sea level pressure After one to two weeks circulating red cell concentration and total body hemoglobin of the babies nursed by intermittently hypoxic mothers were greater than those of babies nursed by control mothers kept at sea level pressures Erslev repeated Carnot s experiments using exceedingly large amounts of plasma from bled rabbits and observed a significant rise in reticulocytes Rabbits receiving repeated injections of plasma from anemic rabbits had increases in red cell count and hematocrit values in peripheral blood and in per cent of nucleated red cells in bone marrow The nature and site of production of hemopoietine are unknown Presence of oxygen is said to diminish erythropoietic activity of plasma taken from anemic animals

Evidence for Humoral Regulation of Erythropoiesis Studies on a Patient with Polycythemia Secondary to Regional Hypoxia reported by Frederick Stohlman Jr Charles E Rath and John C Rose[6] (Georgetown Univ) provided an opportunity to evaluate the effect of blood oxygenation on erythropoiesis

Negro girl 18 with hypertension (160/130) whose health had been excellent except for one episode of hemoptysis was studied clinically and at autopsy Laboratory and histologic studies indicated that polycythemia had developed secondary to hypoxia arising from reverse flow of unoxygenated blood into the arterial circulation via a patent ductus arteriosus The major portion of flow was channeled distally producing decreased O content and Po (O pressure) in femoral arterial blood and presumably that of the descending aorta distal to the ductus Arterial blood to neural centers pituitary and marrow from branches of the aorta proximal to entrance of the ductus had a normal O saturation and Po with increased O content because of the polycythemia Other areas of marrow receiving blood from the distal aorta were hypoxic

(6) Blood 9 721 732 J ly 19 4

Hypercellularity and normoblastic hyperplasia in both aspiration and autopsy sections of sternum and costal marrow where O saturation and Po were normal cannot be explained by a direct effect of hypoxia on marrow but are consistent with a theory of humoral regulation of red cell production Hypoxic polycythemia without neurologic lesions and with normal oxygenation of vegetative centers seems to exclude a neural basis Since blood supplying the pituitary was normally oxygenated apparently increased production of a pituitary erythropoietic hormone is not the primary lesion

Two interpretations suggested for the unexpected relative hypoplasia in iliac marrow are that (1) hypocellularity was a coincidental local finding of little significance or (2) local anoxia was severe enough to prevent response of erythroid cells to the humoral stimulus Neither explanation alters the basic conclusion that erythropoiesis in hypoxic states is regulated by a humoral factor

Observations on Nature of Erythropoietic Serum Factor *(humoral factor) found in the plasma of bled rabbits* and the effect of nitrogen mustard on the ability to produce this factor are presented by Allan J Erslev and Paul H Lavietes[7] (Yale Univ) Once a day for four days 34 rabbits received each 50 ml serum or plasma from donors kept anemic for 24 hours to 8 weeks all with a hemoglobin concentration of less than 7 Gm /100 ml Ten received the same volume of normal serum or plasma from donors with normal hemoglobin concentration Serum or plasma from anemic donors induced a moderate but definite reticulocytosis Normal serum or plasma had no significant effect No significant difference in reticulocyte response was observed whether heparinized plasma or serum from anemic donors was used Four rabbits each received 200 ml of 0 85% saline containing gamma globulin from 200 ml serum from anemic donors and seven received the same amount of serum proteins other than gamma globulin There was no significant difference between reticulocytosis induced by serum from anemic donors and that induced by saline containing albumin alpha globulins and beta globulins from this serum Gamma globulin failed to induce reticulocytosis Se

(7) Blood 9 1055 1061 Novembe 1954

rum kept at 4 C or at —20 C for one to two months ap peared as active as freshly drawn serum

Five rabbits received 200 ml serum from donors given an injection of 1 7 mg /kg nitrogen mustard four hours be fore being made rapidly anemic by bleeding Average hemo globin concentration of the donors at death was 5 7 Gm Three received 200 ml serum from donors given an injec tion of 3 3 mg /kg nitrogen mustard before being made anemic Average hemoglobin concentration of donors at death was 5 9 Gm Mean reticulocyte response in these two groups was almost identical and did not differ significantly from that of controls

Thus serum and plasma from anemic rabbits contains a factor capable of inducing reticulocytosis when injected into normal animals This erythropoietic factor seems to be attached to or behave like a serum albumin alpha globulin or beta globulin Its production was not inhibited by dam age of lymphatic and hemopoietic tissues by nitrogen mus tard

Polycythemic Response in Normal Adult Rats to a Non protein Plasma Extract from Anemic Rabbits was tested in two independently conducted assays by Henry Borsook Ashton Graybiel Geoffrey Keighley and Emanuel Windsor [8] In the first series no significant changes were noted until one week after daily injections of deproteinized plasma filtrate were begun Then both hemoglobin and hematocrit values increased proportionally male animals responding more slowly than females Controls showed no statistically significant changes throughout the experiment To test the possibility that increases in hemoglobin and hematocrit volume might be due to hemoconcentration plasma volume was determined on experimental and control males and fe males about four weeks after injections were begun Blood volume was not significantly different in the two groups if anything experimental animals had a somewhat larger volume Since hemoglobin and hematocrit values are con centrations larger blood volume tended to reduce these values The increases observed in the experimental groups clearly could not have been an expression of hemoconcen tration

(8) Blood 9 734-742 July 1954

In the second series results were clearcut in both males and females Except for the initial reticulocyte counts values for control male animals were uniform throughout a 14 week period Failure of these values to increase in young growing rats may have been due to blood loss Values in experimental animals rose shortly after administration of plasma extract and fell to control level shortly after injections were stopped The increase though not great was significant partly because of the temporal relations which suggest cause and effect and partly because the increase was over normal values Response was greater in females than in males Spread between control and experimental values was exaggerated because blood loss produced a noticeable effect in controls Counts on granulocytic and erythroid elements in femoral bone marrows of female rats at the time they were killed showed insignificant differences in control and experimental groups

The erythropoietic response was comparable to that induced by hypoxia The findings suggest that a humoral factor was at work which was capable of disturbing physiologic mechanisms that establish equilibrium between red blood cell formation and destruction

Production of Polycythemia in Hypophysectomized Rats by the Pituitary Erythropoietic Factor (PEF) is reported by A N Contopoulos S Ellis M E Simpson J H Lawrence and H M Evans[9] (Univ of California) This factor has been shown to repair anemia in hypophysectomized rats and induce an excess volume of red cells in normal animals

Female rats of the Long Evans strain were hypophysectomized at age 26-28 days and maintained for at least 45 days to allow for development of characteristic post hypophysectomy anemia Injection of 0 1 mg PEF daily for 14 days not only repaired anemia but produced hematologic values (hemoglobin hematocrit and red cell volume) exceeding those of normal controls (table) Red cell volume was about 25% higher than normal and 115% higher than in hypophysectomized controls Hematocrit values were also 25% above corresponding normal control values and 100% above values for hypophysectomized controls Peripheral blood of the hypophysectomized rats given PEF

(9) E docr logy 55 808 812 Decembe 1954

also showed stimulation of red cell by an increase in reticu locytes and presence of circulating immature red cells Bone marrow in the femur was vascular and cellular in contra t with the pale fatty marrow of controls

Since none of the known pituitary tropic hormones even when given at high levels over a long period has been able to achieve this result production of polycythemia in

PRODUCTION OF POLYCYTHEMIA IN HYPOPHYSECTOMIZED RATS BY PITUITARY ERYTHROPOIETIC FACTOR

	H ophy c omize R s		No m Co ols
	C t ls	G en PEF	
No rats	7	6	7
Body weight Gm	84±2	87±2 5*	205±6
Hemoglobin Gm /100 ml	10 3±0 3	12 3±0 3	12 9±0 3
Hemoglobin/100 Gm body weight Gm	0 50±0 01	0 61±0 01	0 65±0 01
Hematocrit %	27 7±1.2	57.3±3 5	45 5±1.3
Total red cell vol ml	1 14±0 10	2 52±0 17	4 80±0 15
Red cell vol /100 Gm body weight ml	1 36±0 08	2 90±0 12	2 34±0 05

St d d $\sqrt{\frac{d}{(-1)}}$

hypophysectomized rats has been interpreted as additional support for the concept that the PEF 1 a substance distinct from all other hypophysial hormones

[The conclusions reached here depend somewhat upon semant cs To the authors the increases of total red cells and of hemoglobin are taken as evidence of polycythemia To this editor however polycythemia in the physiologic ense of increased oxygen carrying power in the circu lating blood does not exist unles the hemoglobin concentration is in creased above normal Here in the treated animals the hemoglobin concentration has been returned to normal but no more If the red cells are slightly hypochromic the increased red cell volume and hematocrit with normal hemoglobin are readily understood as for example in the anemia of thalassemia minor which in its day has been erroneously reported as familial polycythemia More impressive evidence than this for an erythropoietic factor of endocrine origin is g ven in the article by B J Kennedy and I T Nathanson (J A M A 152 1135 1141 1953) in which intens ve androgen therapy is reported to have induced sus tained hemoglob n levels as high as 19 Gm % in patients with metastatic brea t cancer This alone however cannot be taken as evidence that this is the way in which erythropoiesis is normally controlled —Ed.]

Significance of Dry Tap Bone Marrow Aspirations Under certain conditions when little or no marrow (dry tap) is obtained on aspiration the scanty yield is attributed

to faulty technic or marrow aplasia That the difficulty may be due to involvement of the marrow by pathologic tissue and should be further investigated was demonstrated by surgical trephine marrow specimens obtained by Austin S Weisberger[1] (Western Reserve Univ) from 24 consecutive patients after repeated attempts at aspiration had resulted in dry taps Metastatic carcinoma was found in the marrow sections in six lymphosarcoma in four Hodgkin s granuloma in five sarcoid in two histoplasmosis and miliary tuberculosis in one each and extensive fibrosis in five In the last five metastatic carcinoma was found in the marrow of one at autopsy typical acute monocytic leukemia developed in two Hodgkin s disease was found in one on lymph node biopsy and the condition remained undiagnosed in one

Although abnormalities were present in each trephine sample areas of normal marrow were present in the patients with histoplasmosis and miliary tuberculosis In the other samples normal marrow architecture was almost completely obliterated by the pathologic lesion Bone marrow aspiration established the diagnosis in five cases previously undiagnosed

Fibrosis was the commonest alteration of the marrow associated with dry taps and was usually associated with carcinoma Hodgkin s disease or other granuloma Extensive fibrosis in the sections obtained does not exclude the presence of carcinoma or granuloma elsewhere A fibrotic reaction may even precede or accompany an acute leukemic process Dry taps or scanty yields may also be obtained in agnogenic myeloid metaplasia aplastic anemia and occasionally in pernicious anemia and acute leukemia In pernicious anemia and acute leukemia this may be attributed to increased cellular density of the marrow and to the cohesiveness of immature cells

Hemotoxic Reactions to Drugs are increasingly common According to William Dameshek[2] (Tufts College) history of each hemotoxic drug follows an almost classic pattern First there are only occasional cases of severe anemia leukopenia thrombopenia or pancytopenia Then

(1) Am J M Sc 29 63 68 J ry 1955
(2) P tg ad M d 16 369 380 N mbe 1954

comes a shower of similar cases thereafter as physicians become aware of the danger the drug is used less and less and reactions subside

In 1916 Selling demonstrated in animals that benzene caused hypoplasia and aplasia of marrow with reflected changes in red cells white cells and platelets of peripheral blood In 1922 agranulocytic angina or agranulocytosis was proved to be fundamentally a drug reaction with aminopyrine most often the cause Other drugs later incriminated as granulocytopenic include novaldin® causalin (aminopyrine and hydroxyquinoline) dinitrophenol sulfapyridine thiouracil propylthiouracil tapazol® and butazolidin® Even antihistamines have induced agranulocytosis Chloramphenicol and streptomycin have produced leukocytopenia

Drugs act on red blood cells by destroying erythropoietic function of marrow or by injuring the circulating red cells directly or by an autoimmunization mechanism Such direct acting hemolyzers include acetanilid phenylhydrazine sulfanilamide naphthalene and p dichlorobenzene [Fuadin® clearly may induce hemolytic anemia by sensitizing the red cells —Ed]

Thrombopenia usually represents part of a pancytopenic response by marrow to prolonged or intensive exposure to the offending drug There may be an initial thrombopenic effect induced by destruction of marrow megakaryocytes later accompanied by other hematologic signs Sedormid® thrombopenic purpura however was proved due to development of a drug platelet antibody which on additional dosage resulted in a violent reaction with platelets in the circulation and megakaryocytes in the marrow acting as shock organs Quinidine may also attach itself to the platelet which may act as an autoantigen A highly specific autoantibody develops which does not react with platelets themselves but produces marked agglutination in the presence of quinidine Quinidine probably acts as a hapten becoming fully antigenic in the presence of platelets

In generalized marrow reactions initially only one element may be affected so that thrombopenia or granulocytopenia appears before development of aplastic anemia Pancytopenic drugs probably cause highest mortality as they

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(2) P tg ad Med 16 369 380 N mber 1954

as adjuvants A combination of these measures should be used in pancytopenia

Dameshek suggests these commandments for use of drugs (1) Do not use a drug unless it is essential (2) Do not use potentially toxic drugs unless the need is im pelling (3) Investigate the formula (4) Be alert for such side effects as fever joint pains and skin eruptions (5) Do not rush into powerful and possibly harmful therapy

[An excellent summary with sage advice—Ed]

Studies on the Nature of Radiation Protection Factor in Mouse Spleen are presented by L J Cole M C Fishler and M E Ellis[3] (San Francisco) Prior studies by Jacobson and others have shown that survival of mice exposed to lethal whole body irradiation is markedly increased by sub sequent peritoneal implantation of normal spleen tissue The same effect was obtained with intraperitoneal or intra venous injection of fresh normal spleen homogenates given as long as 45 hours after exposure Enhanced hemopoietic regeneration was associated with better survival By use of mouse spleen homogenates of various subcellular elements separated by differential centrifugation it was found that the protective activity lies in the nuclear fraction Experi mental evidence suggests that the disturbance elicited by ionizing radiations may be an aberration in the chain of metabolic events leading to the biosynthesis or utilization of nucleoprotein and that the protective factor is a desoxyribo nucleoprotein The factor was found to be inhibited by desoxyribonuclease and trypsin but not by ribonuclease

The authors evaluated the effect of dialysis heat and certain metabolic inhibitors on the protective activity of mouse spleen homogenates The factor was nondialyz able through cellophane membranes suggesting that it is of a high molecular weight Exposure of homogenates to normally denaturing temperatures resulted in loss of pro tective activity The addition of sodium fluoride to the homogenates retarded the loss of activity on incubation at 37 C for one hour Since this compound is known to be an inhibitor to desoxyribonuclease it suggests also that the factor is a desoxyribonucleoprotein Adenosine triphosphate increased the stability of the spleen factor

Bone marrow has been shown to have an action similar

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often produce irreversible reactions in the marrow Among these are benzene benzedrine® tridione® mesantoin® quinacrine and chloramphenicol

Antileukemic and antileukosarcoma drugs particularly aminopterin and triethylene melamine (TEM) are more myelotoxic than the other drugs mentioned, but their use can be justified in such desperate conditions as leukemia and generalized leukosarcoma

Mechanisms of hemotoxicity are thus a direct effect on one or more types of marrow or blood cells or an indirect effect mediated through development of an immune body In addition some individuals seem to have allergic susceptibility to a given drug [Susceptibility to primaquine is due to individual lack of reducing substances (glutathione) in the red cells —Ed]

Importance of a drug s formula in causation of agranulocytosis was emphasized by Kracke who believed that the benzene ring combined with N NH or NH_2 was highly toxic to white cells Almost all the hemotoxic drugs show such structures Possibly the greatest toxicity occurs with drugs having the most N groups e g aminopterin and TEM Tridione® and mesantoin® have similar structures but the latter has two N s and has higher hemotoxicity Aminopyrine with three N s is more hemotoxic than aspirin which has none Even chloramphenicol which has a relatively large molecule and is not an aniline product but a soil antibiotic has a nitrite group linked to a benzene ring Quinidine an alkaloid derivative has a double benzene ring structure with an NH group Thus the chemical structure may give a clue to hemotoxicity of a new drug This is not necessarily reliable since phenobarbital which is not hemotoxic contains a benzene ring and NH groups

Prevention of hemotoxic reactions is best accomplished by restricting the use of potent drugs to conditions with impelling indications Side effects should be watched for Continued treatment requires blood examinations with particular attention to eosinophilia and leukopenia In treatment of hemotoxic reactions the most important step is to stop the drug at the first sign of abnormality Specific measures include transfusions for hemolytic anemia large doses of penicillin for granulocytopenia fresh blood transfusions for thrombopenia with corticotropin and [illegible]

as adjuvants A combination of these measures should be used in pancytopenia

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(3) Radiology 64 201 209 February 1955

to pleen in protection against radiation The authors eval uated the protective ability of homogenates obtained from other mouse tissues Thymus and liver homogenates gave no protection against lethal radiation in mice and homog enates of skeletal muscle lungs and heart muscle may even enhance mortality Since thymic lymphoid tissue is similar to that of the spleen it appears that the protective factor is not of lymphoid origin

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Blood showed greater interdisease variation than did marrow Pertussis was notable with the highest mean leukocyte count of 17 000/cu mm including 69 5% lymphocytes Scarlet fever and poliomyelitis showed the greatest tendency to eosinophilia all diseases except poliomyelitis showed a tendency to peripheral granulocytic immaturity A leukopenic trend was evident in measles

Consideration of theories of increased peripheral destruction vs decreased marrow formation led to the opinion that either or both are possible in individual cases

Is Liver a Tonic ? Short Study of Injecting Placebos Many doctors believe that some nonanemic patients feel better after receiving liver and vitamin B_1 and there have been conflicting reports about the effects in healthy and underweight children when these substances were administered

J R O Brien[5] compared the subjective effect of injections of a liver extract (plexan) and vitamin B_{12} with that of saline in four groups of patients Ampules were colored indistinguishably and identified by a random number No blood studies were made and patients with signs and symptoms of anemia were excluded

There were four groups of volunteers (86 patients) In group I were young men with active tuberculosis from

(5) B r M J 2 136-137 J ly 17 1954

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(4) Acta h m t. 12 293 304 1954

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(5) B M J 2 136 137 July 17 1954

one ward in group II middle aged or aged patients male and female in a chronic ward for various diseases in group III middle aged orthopedic outpatients attending a physiotherapy department usually for rheumatoid arthritis and in group IV private outpatients of varying sex and age who asked for a tonic Injections varied from one to six and were usually given at weekly intervals

Results are summarized in the table Differences among the groups are explained by degree of suggestibility of the patient or degree of suggestion employed by the doctor In group I the doctor was strictly neutral explaining that

ANSWERS TO QUESTION HOW DO YOU FEEL?

		G up I		Group II		G o p III		Group IV		Tot l	
		/	No		No		No		No		No
Plexan	Better	11	1	14	3	69	9	70	23	48	36
	S me	78	7	81	17	31	4	24	8	48	36
	Wo se	11	1	5	1	—	—	6	2	4	4
Vitamin B_{12}	Better	17	3	23	3	64	7	73	24	49	37
	S me	83	15	77	10	27	3	24	8	48	36
	Worse	—	—	—	—	9	1	3	1	3	2
Saline	Bett r	16	3	16	2	64	9	61	19	43	33
	Same	79	15	84	10	29	4	29	9	50	38
	Worse	5	3	—	—	7	1	10	3	7	5
Total	Bett r	15	7	16	7	66	25	68	66		
	Sam	81	37	82	37	29	11	26	25		
	Wo e	4		2	1	5	2	6	6		

this was a trial the patients were probably less suggestible than those in other groups In group II the doctor selected from a chronic ward patients he thought to be reliable and asked them to try to distinguish among the injections some supposedly a tonic In group III no mention was made of a tonic and the patients assumed that the injections were for rheumatism The improvement may have been due to the general air of optimism in a physiotherapy department dealing with a chronic disease In group IV the patients had asked for a tonic thus declaring themselves mentally unwell

More improvement was reported by females in groups II and III probably due to the greater suggestibility of women No sex difference was noted in group IV The greatest improvement was in the subjective senses of well being and energy rather than in appetite and sleep habits

It is apparent that the patients were unable to distinguish among injections of liver vitamin B_1 and saline

[Comment is superfluous —Ed]

HEMOLYTIC ANEMIAS

Clinical Pathology in General Practice Investigation of Hemolytic Anemia is described by John F Wilkinson[6] (Univ of Manchester) In general acute or subacute hemolytic anemias have extrinsic causes Most chronic types have familial or hereditary features and the red cells themselves may be abnormal e g acholuric jaundice and familial hemolytic spherocytic anemia sickle cell anemia and thalassemia Acute hemolytic anemias may be caused by toxic or hemolytic effects on normal red cells in severe bacterial or protozoal infections e g septicemia and malaria Many chemical poisons and such agents as saponin lysolecithin snake venom and Vicia fava have similar effects Severe acute hemolytic anemias also arise from incompatible blood transfusions production of anti Rh agglutinins (causing erythroblastosis fetalis) and in the presence of cold isohemolysins Acute or subacute hemolytic anemia may also be secondary to Hodgkin s disease carcinomatosis hypersplenism and leukemias

With all hemolytic anemias there are variable jaundice and excessive red cell destruction hemorrhagic or hemolytic signs and pigment gallstones are common Pyrexia malaise headaches and hemoglobinuria may be noted the spleen is often enlarged the liver less often and occasionally the lymph nodes Glossitis neurologic symptoms and signs and flatulent dyspepsia are absent Essential laboratory studies in diagnosis of hemolytic anemia include a full blood count with estimation of reticulocytes daily and of osmotic fragility of red cells marrow biopsy gastric analysis and search for abnormal agglutinins in blood Subsidiary tests may include fecal and urinary urobilinogen and special tests for specific agglutinins or other hemolytic factors

The cause of the hemolytic state in a variety of diseases

(6) B t M J 1 1430 143 J 19 1954

is antibodies against the patient s own red cells (autoanti bodies) In many cases no reason for this can be demonstrat ed but in others an associated disease is found e g reticu loses chronic lymphatic leukemia Hodgkin s disease peri arteritis nodosa and disseminated lupus erythematosus The abnormal antibody in most cases of acquired hemolytic dis ease is a hemagglutinin which can be demonstrated by the Coombs test Agglutination will not take place in saline To identify such antibodies Coombs prepared an anti hu man globulin serum by injecting human globulin into rab bits When red cells sensitized by a nonagglutinating anti body are washed in saline and then suspended in the anti globulin serum they become agglutinated

In most cases of idiopathic acquired hemolytic anemia the Coombs test gives positive results Agglutination may also be demonstrated by suspending the cells in a colloid (bovine albumin) Trypsinized red cells are also good in dicators of incomplete antibodies and do not require a protein medium for agglutination Many of the abnormal incomplete agglutinins are hemolytic when incubated with complement against trypsinized red cells

Reticulocytosis with anemia in the absence of hemor rhage or liver and iron therapy and persisting for weeks or months despite treatment is almost pathognomonic of hemolytic anemia Significant increase in red cell osmotic fragility is characteristic but does not indicate the type of hemolytic anemia Platelet count is usually normal but may be decreased with hemorrhage Sickle cells are dem onstrated by sealing a drop of blood under a cover slip to reduce oxygen tension Numerous target cells indicate *thalassemia*

Marrow biopsy helps to exclude leukemia pernicious anemia and other conditions with similar clinical and blood findings In hemolytic anemia there is marked hyperplasia with large numbers of early basophilic intermediate and late normoblasts Proerythroblasts may also be increased In chronic hemolytic anemias myeloid erythroid ratio is often under unity with total nucleated red cells 60-80% of the total nucleated count Megaloblasts are rarely found

In hemolytic jaundice indirect van den Bergh reactions or direct delayed reactions are obtained in toxic action

on the liver a biphasic reaction may occur Small increases in serum bilirubin to 1 or 2 mg /100 ml are usually significant When intravascular hemolysis is rapid hemoglobin and methemalbumin are found in peripheral blood Hemoglobin appears in urine when plasma level is over about 130 mg /100 ml

[This is a good general description of the problem In the next article are more clinical and laboratory details —Ed]

Diagnosis and Management of Acquired Hemolytic Anemia G C de Gruchy[7] (St Vincent s Hosp Melbourne) reports 22 cases (21 in women) of autoimmune acquired hemolytic anemia Twelve were idiopathic and 10 symptomatic (carcinoma of liver reticulosarcoma following phenylbutazone therapy ovarian cyst 1 each lupus erythematosus proved in 2 probable in 2 rheumatoid arthritis 2 In eight of the latter the primary disease was apparent before onset of hemolytic anemia Necessity for a careful search for an underlying disease especially lupus erythematosus in all cases of hemolytic anemia is stressed Clinical features were greater incidence in females (21) and frequency of constitutional symptoms and associated infections (12 cases) Jaundice was absent in six and the spleen was enlarged in all but two

A positive response to the Coombs test established the autoimmune nature of the hemolytic process although the result was invariably positive at some stage in all patients tested it was initially negative in three and became negative in two after steroid hormone therapy After splenectomy it usually remained positive regardless of clinical result A false positive Wassermann reaction occurred in 4 of 16 patients tested

ACTH in adequate doses (average 50 100 mg /day) is the initial treatment of choice if no response occurs cortisone (average dose 100 200 mg /day) should be tried as some patients respond to one and not to the other Blood transfusions should be used when necessary to maintain life but because of reactions should be kept to a minimum Splenectomy is indicated for patients refractory to steroid hormone therapy and probably also for those who require large maintenance doses to control the anemia Splenectomy

(7) A t la A n M d 3 106 115 M y 1954

was performed on 12 patients 5 had complete remissions lasting 6 33 months 2 had short partial remissions and 5 showed no clinical response (3 of these were idiopathic) The Coombs reaction became negative after splenectomy in only one

Six women died One 62 had cerebral thrombosis and carcinoma of the liver was discovered at autopsy Another 64 died of the primary reticulosarcoma One 58 had a coronary occlusion after complete remission for six months after splenectomy One 38 died in acute relapse four months after splenectomy A girl 13 with idiopathic anemia showed no response to splenectomy or exsanguination transfusion but had a spontaneous remission for three months after 22 5 L blood had been given in eight weeks She died of rupture of an old hematoma at the splenectomy site One patient 61 died after transfusion reaction autopsy revealed the first evidence of an ovarian dermoid cyst and spleen of normal size

Spontaneous remissions are frequent especially in chronic cases hence treatment results are difficult to assess No patient can be regarded as permanently cured if the Coombs reaction remains positive even though hemoglobin reticulocytes and serum bilirubin values are normal Possibility of relapse always remains particularly during infections In secondary cases prognosis depends largely on the underlying disease which in many instances is itself fatal

Simplified Method for Preparation of Antihuman Globulin (Coombs) Serum Nicholas J Menolasino and Israel Davidsohn[8] (Chicago Med School) heated rabbit serum diluted with physiologic saline at 65 75 C to eliminate interfering hemagglutinins to human erythrocytes replacing the tedious and expensive absorption method of processing diagnostic serum The method is based on previous observations by others Prasek reported that rabbit immune agglutinins produced against pigeon guinea pig and horse erythrocytes are considerably more thermostable than naturally occurring hemagglutinins for the same antigens in normal rabbit serum Serum diluted with physiologic saline does not coagulate when heated to relatively high temperatures Specificity and stability of the antiglobulin antibody are not affected

(8) Am J Clin Path 24 1205 1210 October 1954

This is a simple and inexpensive method for production of Coombs serum and much time is saved in running test titers on animals to be bled Need for a ready supply of fresh A B and O erythrocytes is eliminated Washing large volumes of cells for a long time is not required The heating procedure also dispenses with hemolysis of serums because of elimination of absorption with more or less fragile red cells A further advantage is elimination of trace constituents of specific and nonspecific proteins from absorption with the blood cells

[Consult the original article for details —Ed]

Autohemolysis and Other Changes Resulting from Incubation in Vitro of Red Cells from Patients with Congenital Hemolytic Anemia were studied by J G Selwyn and J V Dacie[9] (Postgrad Med School London) by means of volume changes osmotic fragility and cation contents of red cells incubated in serum at 37 C for 24 and 48 hours Incubation of sterile defibrinated blood from patients with hereditary spherocytosis results in a more rapid increase in osmotic fragility of the red cells and a faster rate of hemolysis than normal The cause of these unusually rapid changes lies in the red cells Results showed that spontaneous autohemolysis is due not to progressive swelling of cells but probably to degenerative changes in cell membranes On incubation normal red cell volume increases in the first 24 hours due to gain in sodium and water cells lose potassium but more slowly than they gain sodium In the second 24 hours loss of potassium exceeds gain in sodium and cells shrink to near their original volume These cation changes and autohemolysis are greatly reduced if glucose is present throughout the 48 hours of incubation

In hereditary spherocytosis rates of autohemolysis of increase in osmotic fragility and of potassium loss are greater than normal Continued presence of glucose during incubation markedly retarded these changes In hereditary elliptocytosis trait red cells behaved normally In one case of elliptocytosis with hemolytic anemia autohemolysis was normal but there was increased potassium loss In another patient with hemolytic anemia and increased osmotic fragility autohemolysis was greatly increased glucose reduced autohemolysis moderately Incubation distinguished

(9)—B 9 414-438 M y 1954

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(8) Am J Cl n P th 24 1205 1 10 Oct ber 1954

type 2 was distinguished from that of hereditary spherocytosis by absence of beneficial effect of added glucose Lysis of type 1 cells could be distinguished from that of normal cells by the smaller effect of glucose These technics can also be useful in differentiation of anemias of obscure origin from those due to congenital red cell defects

[These observations presumably have a fundamental bearing on the hemolytic functions of the spleen where it has now been well established that sequestration of red cells and separation from plasma characteristically occur —Ed]

Hereditary Nonspherocytic Hemolytic Disease Study of a Singular Familial Hemolytic Syndrome In contra t to the striking peripheral blood picture of sickle cell anemia Mediterranean anemia hereditary spherocytosis and hereditary elliptocytosis no consistent morphologic abnormality of the red cells has been recognized in patients with this disease Arno G Motulsky William H Crosby and Henry Rappaport[1] (Armed Forces Inst of Pathology) report studies on four cases from three unrelated families

Hereditary nonspherocytic hemolytic disease seems transmitted as a mendelian dominant In some cases the hereditary mechanism may be a recessive gene from each parent The basic erythrocytic defect is unknown The disease may be a group of diseases involving more than one mechanism

Red cell survival time studies revealed an intraerythrocytic defect with a mean life span of 12 17 days in the authors cases Normal transfused red cells survived normally Anemia was normochromic and normocytic or macrocytic Osmotic and mechanical fragility of the red cells was normal fragility tests after incubation at 37 C for 24 hours showed a mild increase compared to normal in some Autohemolysis of incubated oxalated blood was not marked but varied Electrophoretic mobility of hemoglobin was normal small increases of fetal hemoglobin were seen occasionally

In contrast to the histologic findings in hereditary spherocytosis splenic pulp was not congested but hemosiderin deposits were heavy Liver biopsy showed deposits of hemosiderin in parenchymal and Kupffer cells Splenectomy did not arrest the hemolytic process although mild improvement was seen in one case

(1) Blood 9 749 77 A g t 1954

two distinct types of congenital nonspherocytic hemolytic anemia In two patients with type 1 autohemolysis osmotic *fragility and cation changes on incubation were normal* glucose had a normal effect on fragility and cation changes but reduced autohemolysis only slightly In two patients with type 2 autohemolysis increase in osmotic fragility and potassium loss were markedly increased Glucose did not retard any of these changes and cells were unable to utilize glucose at the normal rate

The nature of degenerative changes affecting incubated red cells and whether substances in serum affect this process are unknown Lytic substances such as lysolecithin have been *extracted from incubated serum and red cells* before extraction they are probably combined with proteins or lipids and are present only as weakly lytic complexes

Continued presence of glucose enables expulsion of sodium from normal cells to continue and so improves cation efficiencies Improvement in sodium efficiency on addition of glucose is thought to be an index of control of sodium by cells Sodium metabolism of hereditary spherocytes and cells of nonspherocytic congenital hemolytic anemia type 1 and of hereditary elliptocytes is normal Conversely sodium efficiency of antibody coated spherocytes in a case of acquired hemolytic anemia was below normal in the presence of glucose presumably because cells were irreversibly damaged by the antibody Reduction of lysis by glucose is not due to lowering of pH by lactic acid although increased acidity plays a part Splenectomy did not benefit the two patients with type 2 nonspherocytic anemia and glucose did not improve in vitro lysis or one patient with type 1 nonspherocytic anemia in whom glucose only slightly improved normal rate of autohemolysis Conversely splenectomy corrected anemia in hereditary spherocytosis and the effect of glucose in vitro was marked

In vitro studies seem to have diagnostic value The 48 hour autohemolysis in sterile defibrinated blood was constantly increased in cases of hereditary spherocytosis as was osmotic fragility of the most fragile cells after 24 hours incubation Rate of autohemolysis was one of the main distinctions between types 1 and 2 of atypical congenital nonspherocytic hemolytic anemia Increased autohemolysis of

cellular defect was demonstrable in family members Of the six elliptocytics only the infant was anemic

This is the second reported instance of probable homozygosity for the elliptocytic trait which is known to occur in 0 02 0 04% of the population It is important to recognize that this genetic entity exists in three states (1) asymptomatic elliptocytic carrier state (normal cell survival) (2) asymptomatic elliptocytic state with compensated hemolysis (cell survival somewhat shortened) and (3) elliptocytic hemolytic anemia which may be heterozygous homozygous or possibly associated with another abnormal gene (cell survival markedly shortened)

↓ The next two articles conclude a series of observations successfully analyzing the nature of the red cell defect leading to susceptibility to lysis by oxidant drugs —Ed

Hemolytic Effect of Primaquine—*VI In Vitro test for sensitivity of erythrocytes to primaquine*—When primaquine is given to sensitive men an acute hemolytic anemia develops due to an intrinsic defect of the erythrocytes which are also sensitive to phenylhydrazine acetanilid sulfanilamide phenacetin thiazolsulfone and certain related compounds Sensitive erythrocytes appear to constitute a distinct blood group identifiable morphologically immunologically by hemoglobin type or with respect to fragility to various agents

Previously Ernest Beutler Raymond J Dern and Alf S Alving[3] (Univ of Chicago) demonstrated that primaquine caused considerably greater Heinz body formation in the blood of sensitive than of nonsensitive men These bodies apparently consist of denatured proteins and are a manifestation of red cell damage Several agents will cause formation of Heinz bodies under suitable in vitro conditions In response to the need for a simple in vitro test to identify sensitive cells accurately the following standardized test was developed

METHOD—With a 0 1 ml blowout pipet 0 1 ml whole blood was added to 2 ml of 100 mg % acetylphenylhydrazine solution in a test tube (inner diameter 12 mm) The suspension was immediately mixed and aerated two or three times by drawing approximately 0 1 ml into the pip t and blowing it and a small quantity of air back into the suspension The pipet was left in the uncapped tube and placed in a 37 C water bath Cell suspension was again agitated

(3) J Lab & Cl Med 45 40 50 J y 1955

Diagnostic difficulties may be encountered with mild cases Examination of rouleaux in fresh blood and an osmotic fragility test in 0 65% sodium chloride after incubation usually establishes the differential diagnosis The condition must be differentiated from erythroblastosis due to Rh or other blood group incompatibilities in the newborn Other hereditary hemolytic diseases such as sickle cell anemia Cooley s anemia hereditary spherocytosis and hereditary hemolytic elliptocytosis are easily ruled out by typical clinical and hematologic manifestations When a family study cannot be done estimation of red cell survival time may be necessary to rule out acquired hemolytic anemia with a negative Coombs reaction Some cases diagnosed as constitutional hyperbilirubinemia (familial nonhemolytic jaundice) may have been mild hereditary nonspherocytic hemolytic disease

[For a report of the effects of in vitro incubation of the red cells in this condition the reader is referred to the preceding article by Selwyn and Dacie —Ed]

Elliptocytosis with Hemolytic Anemia Effects of Splenectomy in a male infant are reported by Farle L Lipton[2] (State Univ of New York)

Child born in October 1952 on the second day had jaundice which decreased during the first week but reappeared soon afterward Blood studies at 1 month revealed marked anemia (3 8 Gm hemoglobin) and a diagnosis of congenital elliptocytic hemolytic anemia was made on the basis of 70% elliptocytes marked erythroid hyperplasia of bone marrow bilirubinemia increased serum iron increased hemolytic index and recurrent normochromic anemia Jaundice and anemia were controlled by transfusions until splenectomy was performed at age 7 months The spleen weighed 65 Gm and an accessory spleen was also removed The specimens showed prominent follicles with some active germinal centers pulp was compressed by dilated and engorged sinusoids No increased iron pigment was found No transfusions were required after surgery and only minimal if any hemolysis continued Morphologic abnormalities in the erythrocytes persisted along with pronounced increases in osmotic and mechanical fragilities Alkali resistance of hemoglobin and electrophoresis were normal The child s growth and development have continued normally in all respects

This infant was believed to be homozygous for the dominant elliptocytic trait The mother and father second cousins of Italian descent are both carriers of elliptocytes as are her mother and sister and his father No other intrinsic

(2) P d atrics 15 67-83 Jan ary 1955

two (46 and 62%) Mean of all test results on nonsensitive men was only 11 9% Interpretation of results on the basis of a dividing line at 32 5% yielded no false negatives and only two false positives

Tests on 18 sensitive and 86 nonsensitive subjects indicated accuracy exceeding 98% in predicting primaquine sensitivity Negative results were obtained on the blood of patients with Hodgkin s disease multiple myeloma thalassemia paroxysmal nocturnal hemoglobinuria polycythemia rubra vera and hemoglobin C S disease

The various test factors were carefully evaluated i e composition and age of buffered acetylphenylhydrazine solution quantity of blood added incubation time and temperature and degree of oxygenation The last particularly has pronounced effect on Heinz body formation which is promoted by oxygen Heinz body formation by phenylhydrazine primaquine hydroxylamine and ascorbic acid in sensitive and nonsensitive cells was also compared The mechanism of Heinz body formation by this group of substances may be oxidation of a red cell component and sensitive cells may be deficient in a protective enzyme system

VII Biochemical studies of drug sensitive erythrocytes are reported by Beutler Dern C Larkin Flanagan and Alving[4] (Univ of Chicago) Erythrocytes from certain persons possess an intrinsic defect which makes them unusually sensitive to the hemolytic action of primaquine phenylhydrazine sulfanilamide acetanilid and certain other drugs In vivo Heinz body formation was more marked in the sensitive cells and only older red cells were destroyed when primaquine was administered In vitro these cells more readily formed Heinz bodies with acetyl phenylhydrazine This suggested that sensitive erythrocytes might have an enzyme or coenzyme deficiency that increases with age

Experiments yielded no indication that sensitivity is due to a defect in glycolysis or in activity of catalase carbonic anhydrase or cholinesterase However primaquine sensitive erythrocytes contain only about 60% the average normal amount of glutathione (GSH) The concept that this deficiency of bound or unbound GSH in the cells is the primary cau e of their unusual sensitivity is strengthened

(4) J Lab & Clin Med 45 286-295 February 1955

and aerated after two and four hours then a small drop (about 0 01 ml) was placed on a cover slip which was inverted onto a micro scopic slide on which a larger drop (about 0 025 ml) of 1% crystal violet in 0 76% NaCl solution had been placed After 5 10 minutes a field in which cells maintained their normal shape and there was little overlapping was selected for oil immersion examination Counts of 100 or 200 erythrocytes were made to determine the per centage containing five or more Heinz bodies When Heinz bodies



F g 59 —He n body f rm t on en t e yth ocyt fter ı c b t w th 100 mg ơ tylphenylhyd ne 1 t f f u h s Wet p pa at o ta ed w th c y t l 1 t ×1 300 (C rt y f Be tler E t l J Lab & Cl Med 45 40 50 J ry 1955)

were present in clusters as many separate granules as could be clearly distinguished were counted Test result was percentage of cells forming five or more Heinz bodies

Appearance of test preparations from sensitive and non sensitive subjects almost always differed sufficiently to per mit them to be distinguished without making counts Most sensitive erythrocytes contained many small Heinz bodies (Fig 59) Nonsensitive erythrocytes generally formed one large well rounded Heinz body 1 2 μ in diameter at the margin When a few smaller Heinz bodies were also pres ent total number did not often exceed four

In blood from sensitive men erythrocytes developing five or more Heinz bodies varied from 45 to 92% (mean 67 8%) in nonsensitive men this varied from 0 to 28% in all but

Canine anti A opsonizes both A_1 and A red cells followed by marked splenic erythrophagocytosis Agglutinating antibodies anti C and anti D were unable to opsonize erythrocytes in vivo or in vitro although red cells exposed to anti C were rendered completely inagglutinable or blocked by canine anti C in one instance Anti dog red cell immune rabbit serum in relatively small doses induced marked erythrophagocytosis in the recipient s spleen and produced hemoglobinemia probably by direct intravascular hemolysis

Although complement hemolysis erythrophagocytosis and intravascular hemagglutination may be important in destruction of incompatible red cells some data in both man and dog indicate still other mechanisms A patient who had received five transfusions was given 500 ml of Kell positive blood after which he had marked hemoglobinemia hemoglobinuria oliguria and azotemia Isoantibody could be demonstrated in vitro only by the indirect antiglobulin test It did not agglutinate Kell positive cells suspended in albumin plasma or fix complement or hemolyze these cells in the presence of complement Nevertheless this antibody produced rapid intravascular hemolysis in vivo In a similar type of hemolytic reaction a dog received six large transfusions of incompatible cells and incompatibility could be demonstrated in vitro only by the indirect antiglobulin reaction this only after three transfusions Donor cells were nevertheless eliminated at greatly increased rates which were not reduced by splenectomy performed before the last transfusion These observations suggest that some isoantibodies can disrupt red cell ultrastructure in vivo by physicochemical processes

The exact nature of biochemical changes induced in red cells by antibodies is unknown Preliminary studies have shown a pronounced derangement of in vitro phosphorus uptake by red cells of an A positive dog transfused with plasma containing canine anti A Red cells of this animal were undergoing rapid destruction Antibodies apparently can produce abnormalities of red cell metabolism these might cause rapid loss of viability or might be merely another manifestation of injury induced directly by the erythrocyte antibody reaction Possibly energy production of the erythrocyte is inhibited by attachment of an antibody to the cell

by the fact that iodoacetate or arsenite which poison sulfhydryl groups caused nonsensitive cells to become as susceptible to in vitro Heinz body formation as sensitive cells

Studies of Mechanisms of Erythrocyte Destruction Initiated by Antibodies described by Scott N Swisher[5] (Univ of Rochester) may shed light on such clinical problems as hemolytic transfusion reactions erythroblastosis fetalis and the autoimmune type of acquired hemolytic anemia At least four destructive mechanisms exist (1) intravascular hemolysis involving complement (2) intravascular hemagglutination with release of lytic substances from ischemic tissues (3) erythrophagocytosis by peripheral leukocytes or tissue macrophages and (4) direct physicochemical injury of the erythrocyte ultrastructure

Seven canine erythrocyte isoantibody systems are closely analogous to several types of human erythrocyte isoantibody reactions and provide means for quantitative in vivo studies on immunohemolytic systems These have been designated A_1 A B C D E and F in order of their demonstration Canine anti A which resembles immune human anti A is a potent in vitro and in vivo lysin of canine A_1 cells When A_1 cells were given to an immunized A negative recipient massive and immediate hemoglobinemia occurred and donated cells disappeared in a linear fashion over three to four days Intravascular complement hemolysis seems to be the principal mechanism whereby this antibody destroys A_1 erythrocytes Canine anti A is incapable of in vitro lysis of canine A cells but does destroy these cells in vivo in an immunized A negative recipient in an essentially exponential fashion Some intravascular lysis occurred but the bulk of cells was destroyed much more slowly than with comparable transfusions of A_1 cells

Castle Ham and Shen have suggested that red cell agglutination in vivo leads to release of tissue hemolysins Canine anti B C and D however strongly agglutinated red cells at body temperature but most examples of these isoantibodies have little or no capacity to hemolyze incompatible cells in vitro or in vivo

Erythrophagocytosis by splenic macrophages induced by canine isoantibodies was investigated by a special technic

(5) Tr A Am Physcia 67 124 13 1954

strated by the use of saline albumin and trypsin technics as well as by the Coombs test Erythrocyte coating anti bodies were not neutralized with human gamma globulin Cortisone therapy did not affect cold agglutinins and eryth rocyte coating antibodies Cold agglutinated erythrocytes have increased mechanical fragility when the cold aggluti nin is present in high titer and this may be directly re sponsible for hemolysis in vivo as in the first patient In cubation at 37 C for 24 hours causes a marked shift to the left in the osmotic fragility curve Study of the serum of one patient for antibodies to Newcastle virus disease and influenza was negative

The relationship of serum hemolysin to cold agglutinins is unknown The author postulates that incomplete cold agglutinins may assume the properties of a hemolysin on proper stimulation which may be temporary or permanent as in the third patient

Woman 67 had a nonproductive cough of two months duration with anorexia vertigo and easy fatigability for a month A grad II systolic apical murmur was heard There was no icterus lymphade nopathy hepatomegaly or splenomegaly Hemoglobin was 9 Gm erythrocyte count 2 900 000 leukocyte count 7 000 and reticulocytes 3 3% There was slight polychromatophilia but no spherocytosis Total serum bilirubin level was 1 1 mg /100 cc The bone marrow showed normoblastic hyperplasia No free hemoglobin was found in the urine A chest x ray was normal At 3 C agglutinins for O Rh negative cells were present in a titer of 1 32 (saline) 1 2 048 (albumin) and 1 1 024 (trypsin) The antiglobulin reaction was 2+ positive Erythrocyte coating antibodies were not neutral ized by 4% human globulin A hemolytic antibody was demonstrated in a titer of 1 32 Hemolysins were demonstrated against trypsin and erythrocytes after 90 minutes at 37 C Mixing a 3% suspension of the patient s wa hed erythrocytes with fresh guinea pig comple ment or fresh AB serum resulted in immediate hemolysis Failure of hemolysis to occur with heat inactivated serum suggested the presence of a hemolytic antibody attached directly to the erythro cytes Cold had no effect on osmotic fragility but incubation for 24 hours at 3 C increased mechanical fragility Incubation at 37 C increased osmotic fragility with hemolysis Treatment with cortisone orally for seven months (300 mg initially and 50 mg daily mainte nance) resulted in a slight increase in red cell count there was no change in cold agglutinins and the antiglobulin test was still posi tive Hemolysins can still be demonstrated on the surface of the erythrocytes by adding complement

[Th author s observat ons ind cate that a cold agglutinin alone is ra ely responsible for chronic hemolytic anem a.—Ed]

surface Hemolysis might then occur when available energy was critically depleted

Several mechanisms involved in destruction of erythrocytes by antibodies may operate simultaneously in some instances The rate depends on quantitative relationships between available antibody and incompatible red cell mass and also on mode of action of the antibody Ability of an antibody to initiate erythrocyte destruction can be adequately defined only by trial in the intact animal rather than in in vitro systems Destruction of erythrocytes initiated by antibodies apparently is as complex as other general body defense mechanisms

[This is a critical analysis of the immediate mechanism of red cell destruction that does not stop with the mere demonstration of antibodies on the cell —Ed]

Cold Hemagglutination in Acute and Chronic Hemolytic Syndromes Anthony V Pisciotta[6] (Marquette Univ) reviews 27 previous and adds 3 cases of autoimmune hemolytic disease associated with cold hemagglutinins and with the characteristic clinical picture attributed to these antibodies Additional data are offered to show that the relation to cold agglutinins may be of two kinds Thus the accelerated destruction of erythrocytes may also be the result of a second antibody which together with complement is capable of causing hemolysis

The three patients showed pallor slight icterus and absence of splenomegaly Raynaud s phenomenon was present in two with cold agglutinin titers of 4 096 and 16 000 In the first patient who had primary atypical pneumonia the course was acute and self limited the Coombs test was negative and no hemolysis was found In the other two the course was chronic and apparently persistent the Coombs test was positive and a hemolysin was found It was active at room temperature required complement appeared to be independent of the cold agglutinin and disappeared following therapy In the third case hemolysin was demonstrated directly attached to the surface of the patient s erythrocytes by the addition of complement to the washed red cells Hemolysis was enhanced by use of trypsinized test erythrocytes

Complete and incomplete cold agglutinins were demon

(6) Blood 10 295 311 April 195

strated by the use of saline albumin and trypsin technics as well as by the Coombs test Erythrocyte coating anti bodies were not neutralized with human gamma globulin Cortisone therapy did not affect cold agglutinins and eryth rocyte coating antibodies Cold agglutinated erythrocytes have increased mechanical fragility when the cold aggluti nin is present in high titer and this may be directly re sponsible for hemolysis in vivo as in the first patient In cubation at 37 C for 24 hours causes a marked shift to the left in the osmotic fragility curve Study of the serum of one patient for antibodies to Newcastle virus disease and influenza was negative

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[The author s observat ons indicate that a cold agglutinin alone is rarely responsible for chronic hemolytic anemia —Ed]

Immunohemolytic Anemia in Kaposi s Sarcoma with Visceral Involvement Only In immunohemolytic anemia red blood cells undergo increased destruction by abnormal anti bodies adsorbed on the cell surface or present in a free state in the serum Hemolytic anemia is fairly common in Hodgkin s disease leukemia (especially lymphatic) and lymphosarcoma and has been reported with sarcoidosis Gaucher s disease and other reticuloendothelioses suppura tive infections involving lymph nodes typhoid fever and tuberculosis disseminated lupus erythematosus and malig nant and nonmalignant tumors It is assumed that tumor tissue forms antibodies or produces substances possibly by tissue breakdown that can give blood cells antigenic quali ties or in some other way cause antibody formation

Johan Martensson and Hans Henrikson[7] (Univ of Lund) report a case of immunohemolytic anemia associated with Kaposi s sarcoma involving only viscera undiagnosed un til autopsy

Man 63 had acute hemolytic anemia with a positive Coombs test which appeared to be idiopathic white cells and thrombocytes were normal He did not respond to blood transfusions ACTH was effective until therapy had to be stopped because of urinary tract infection Four months after the initial acute episode a swollen neck gland was noted biopsy showed only nonspecific lymphadenitis with abundant plasma cells in the parenchyma Despite extirpation of the spleen which showed no specific pathology the anemia pro gressed. ACTH and later cortisone immediately suppressed hemoly sis Superficial lymph nodes grew rapidly after splenectomy but re sponded to roentgen irradiation Biliary colic occurred as a prelude to final deterioration The patient died two years after the first episode of acute hemolytic anemia Autopsy revealed Kaposi s sar coma which had not been considered clinically because there were no skin lesions or suggestive signs and the general condition did not point to malignancy Pathologic changes varied widely some times vessels dominated sometimes only few vessels were seen in sarcomatous tissue Both early and late changes were at times jux taposed Lesions were found in the lymph nodes stomach and in testine and in one lung

That hemolytic anemia can occur with Kaposi s sarcoma is consistent with observations in other reticuloendothelial diseases Two cases have been reported previously The present case demonstrates that Kaposi s sarcoma need not be accompanied by cutaneous manifestations It must be as sumed that angiosarcoma was present though limited in

(7) Act med sc d 150 175 188 1954

extent at the time of the initial hemolysis although en larged lymph nodes were not observed until four month later Changes in a lymph node removed at splenectomy were not extensive and the spleen showed no foci of angiosarcoma This is apparently the first case of Kaposi s sarcoma with serologically proved immunohemolytic ane mia That the angiosarcoma appeared to increase rapidly after splenectomy may be simply incidental but this was also noted in the case reported by Hogeman who discussed the interesting possibility that the widespread angiosarcoma tous tissue might assume the role of the spleen as the organ causing hemolysis by deplasmatization in accord ance with Fahraeus and Bergenhem s theory of splenic function

Treatment of Erythroblastosis Fetalis by Exchange Transfusion Statistical Analysis of Results in 222 cases and in 67 erythroblastotic infants who were untreated or given one or more simple transfusions is presented by Alexander S Wiener Irving B Wexler and George J Brancato[8] (Brooklyn)

Among 36 women having stillbirths caused by Rh en i tization all but one had Rh antibody titers of 16 unit or higher by the albumin plasma conglutination method In the exception unusual antibodies were present since the titer was high by the antiglobulin and enzyme technics

Among mildly affected babies whose mothers had anti body titers of 8 units or less no significant difference in mortality rate was demonstrable in those receiving exchange transfusion and those untreated or given simple transfusions Among severely affected babies treated by exchange trans fusion mortality rate was 15 5 ±2% and in the intreated and simple transfusion group mortality was as igh as 46 4 ±6 2% The difference 28 9 ±6 5% is statistically sig nificant

In exchange transfusions part of the citrated pla ma is removed from bank blood not more than 3 days old v l h has been allowed to sediment in the refrigerator to red the volume to 400 ml Beginning with the withdrawal 50 cc blood equal volumes of blood are withdrawn and in jected In more severely affected babies a second exchange

(8) Pedi tric 45 546-568 Novembe 1954

transfusion is given 24-48 hours after birth Among 78 erythroblastotic infants treated in this way, of whom 53 had mothers with antibody titers above 8 units mortality was only 5 1 ±1 6% Mortality figures include neurologic sequelae as well as deaths

Whenever the maternal antibody titer is above 8 units and the baby is Rh positive exchange transfusion by the radial artery saphenous vein technic is indicated however normal the baby may appear, and even if hemoglobin concentration and icterus index are normal If maternal antibody titer is low exchange transfusion should be performed if the baby exhibits cord icterus index 20 units or over hemoglobin below 15 Gm or a strongly positive direct antiglobulin test Indications for transfusion are stronger if there have been previous severely affected erythroblastotic infants Another strong indication is a primipara who has been sensitized by blood transfusion or injection

A second exchange transfusion should be considered when a previous erythroblastotic baby has been lost or the Rh antibody titer has been extremely high In the absence of these indications a second exchange should be done if the baby has severe manifestations at birth or develops progressively increasing jaundice

Clinical Features of Genetic Variants of Sickle Cell Disease Ernest W Smith and C Lockard Conley[9] report a comparative study of 15 selected cases of classic sickle cell anemia (S S) and 24 cases of variant forms of sicklemia (with 19 added from the literature) There were 11 cases of sickle cell thalassemia (S thal) and 27 of sickle cell hemoglobin C (S C) disease

Sickle cell anemia exhibited remarkably constant clinical features Anemia generally appeared in childhood and was constant throughout life Jaundice was unremitting Typical crises of bone and joint or abdominal pain were frequent and cardiac abnormalities almost invariable Chronic leg ulcers tortuosity of retinal vessels and diffuse bone disorders were frequent Duration of life was short few patients were over 30 and none was over 40

Patients with variant forms of sicklemia in general had

(9) B ll J h Hopkin H p 94 289 318 Ju 1954

much milder disorders Anemia was discovered in childhood in only 21 of the 43 patients and even in these was not con stant Jaundice often subsided and the serum bilirubin level was normal when anemia was not pronounced The most impressive difference between the groups was in the number of target cells Twenty six patients with S C dis ease had more than 50% and some almost 100% The per centage was usually less in S thal but target cells were more numerous than in S S (5%) or thalassemia major

The spleen may be enlarged with S S during the first few years but thereafter atrophies In contrast 30 patients in the variant groups had splenomegaly including 8 with S thal and 20 with S C disease Crises occurred in variant cases much less often than in S S Abdominal pain was rare Bone and joint pain occurred in almost half the patients with S C disease and in all with S thal Disproportionate elongation of extremities was observed in only one variant case Bone abnormalities were extremely mild or absent Conversely aseptic necrosis of humeral or femoral heads (not observed in proved S S) was present in nine variant cases (six of S C disease and three of S thal) Tortuous ret inal vessels were seen in only a few variant cases Three patients with S C disease had intraocular hemorrhages and another unilateral optic atrophy Pulmonary lesions were much less common in variant groups than in S S Hepatic changes in variant cases were mild Central nerv ous system manifestations were as frequent and as severe in variant cases as in S S Significant cardiac abnormali ties were not seen in the absence of hypertension or organic heart disease The renal disorder which may lead to uremia and death in S S was not encountered in the variant groups Renal hematuria was frequent in those with S C disease

Six of eight patients with S C disease who became preg nant had severe hemolytic crises in the last trimester or immediately post partum Severe hemolytic crises also oc curred during pregnancy in two other patients with variant disease Two of three maternal deaths were in patients with S C disease Records indicate that patients with S S have relatively benign pregnancies

[This careful study should be read in the original —Ed]

Thalassemıa Hemoglobın C Dısease New Syndrome Presumably Due to Combınatıon of Genes for Thalassemıa and Hemoglobın C ıs descrıbed by Wolf W Zuelzer and Eugene Kaplan[1] (Wayne Unıv)

Negro boy 6 was dıscovered to have a hypochromıc mıcrocytıc anemıa Iron therapy was ıneffectual and after sıx months he was referred for hematologıc study Morphology of erythrocytes ın drıed blood fılms was strıkıng wıth extreme pleomorphısm and coexıstence of hypochromıc cells and deeply staıned mıcrocytes some of whıch looked lıke mıcrospherocytes Most of the red cells were markedly hypochromıc prıncıpally target cells showıng un usually pronounced demarcatıon of empty appearıng zones from hemoglobın-contaınıng zones Whıle most hypochromıc cells were of normal or ıncreased dıameter and regular contour some were very small almost resemblıng fragments and others were oval ellıptıcal pear shaped or showed taıl lıke projectıons Mıcrospherocytes by contrast were dense round and faırly unıform No nucleated red cells were seen The large hypochromıc target cells frequently contaıned coarse basophılıc ınclusıons Less than 1% of all cells were sıderocytes Granulocytes and platelets were not remarkable. There was no sıcklıng or erythrocytes ın sodıum metabısulfıte prep aratıons Hemolysıs of erythrocytes began at 0 66% salıne and was not complete at 0 12% When ıncubated at 37 C for 18 hours resıstance of red cells to hypotonıc salıne was even greater Serum ıron was 240 µg /100 ml wıth ıron bındıng capacıty of serum 200 µg /100 ml Total serum bılırubın was 0 4 mg /100 ml Fecal urobılınogen excretıon was 3 mg /day Bone marrow showed moderate erythroıd hyperplasıa wıth the polychromatıc normoblast the predomınant erythroıd precursor Only a few cytoplasmıc ınclusıons were found ın normoblasts but sıderotıc granules were demon strated ın 80%

Patıent s mother 31 ın good health had had eıght chıldren by fıve dıfferent fathers She and three of her chıldren had thalassemıa mınor ı e erythrocyte constants ındıcated slıght mıcrocytıc hypochromasıa The patıent s father carrıed the gene for C hemoglobın and hıs blood contaıned 10-20% target cells Three half sıblıngs were hematologıcally normal Patıent s twın sıster had mıld hypo chromıc mıcrocytıc anemıa almost ıdentıcal wıth that of her mother Two younger half sıblıngs who were moderately anemıc also exhıbıt ed the blood pıcture of thalassemıa mınor The mother had a normal A hemoglobın pattern as dıd two half sıblıngs and the twın sıster Patıent s hemoglobın consısted of a mıxture of A and C ın propor tıons of 71 and 29% The father s hemoglobın also contaıned com ponents A and C both by standard Tıselıus technıc and paper elec trophoresıs In both the patıent and hıs mother less than 2% alkalı resıstant hemoglobın F was found

It was concluded that the patıent s anemıa ıs the result of ınteractıon of the gene for hemoglobın C wıth that for

(1) Blood 9 1047 1054 November 1954

thala semia the patient being heterozygous for each No conclusions can be drawn as to whether these genes are allelomorphs Exact mechanism of the anemia also is not clear It is highly probable despite low urobilinogen ex cretion that an element of hemolysis is present but the most striking feature is the hypochromic microcytosis The slight reticulocytosis is puzzling especially in view of the fairly marked erythroid hyperplasia of bone marrow Other noteworthy features are lack of splenic enlargement and coexistence of normochromic or hyperchromic microcytes with decrea ed resistance and hypochromic target cells Thus far the severe anemia has been without crises hepato splenomegaly or skeletal changes

Studies on Abnormal Hemoglobins IX Pure (Homo zygous) Hemoglobin C Disease Since discovery of hemo globin C in 1950 this abnormal pigment has been encoun tered with normal adult (A) hemoglobin in the hemoglobin C trait and with sickle cell (S) hemoglobin in sickle cell hemoglobin C disease (C variant of sickle cell disease) In the e two conditions heterozygosity for hemoglobin C has been postulated and homozygosity for the gene responsible for this pigment might be expected Karl Singer A Zerne Chapman Seymour R Goldberg Herbert M Rubinstein and Sol A Rosenblum[2] report clinical and hematologic features of four patients with pure (homozygous) hemo globin C disease

Two patients were Negro men 22 and 29 and two were Negro sisters 11 and 9 They exhibited characteristic fea tures of (1) a hemolytic process with or without anemia (2) splenomegaly and (3) numerous target cells in the film Clinically the adults revealed a compensated hemolytic process as manifested by an elevated reticulocyte output with normal hemoglobin and red cell levels and no evi dence of bleeding The children had moderate normochro mic normocytic anemia Hyperbilirubinemia was observed in two Existence of a hemolytic process was further con firmed by a survival time study of erythrocytes in one case mean survival being 13 days In other patients with pure hemoglobin C disease the mean red cell life may be some what shorter or the marrow may not always respond maxi

(2) Blood 9 1023 1031 N mbe 1954

mally anemia may then result from either or both causes

Two patients had nonspecific abdominal pain Splenectomy must be considered if splenic enlargement causes pressure Splenectomy in one case did not ameliorate the hemolytic process the histologic picture showed severe congestion Thrombocytopenia in one was attributed to splenic dysfunction The consistent finding of conspicuous numbers of target cells in the film may suggest that erythrocytes containing hemoglobin C tend to leptocytosis This anomaly is not characteristic for presence of hemoglobin C being common in sickle cell anemia thalassemia liver disease and following hemorrhage or splenectomy

With the alkali denaturation technic abnormal amounts

Electrophoresis Pattern	Type of Hgb	Electrophoresis Pattern	Type of Hgb
	A		A
	A+S		A+C
	S		A+S
	A+C		C (Patient)
	C (Patient)		

Fig 60 — Paper electrophoresis patterns of hemolysates of two patients (Courtesy of S g K t l Blood 9 1023 1031 November 1954)

of F hemoglobin were not noted With standard electrophoresis at pH 6 5 a single component having the mobility of hemoglobin C was found in each solution Results with paper electrophoresis of the stroma free hemolysate (Fig 60) furnished objective confirmation of the diagnosis With a buffer of pH 8 6 hemoglobin A moves fastest C slowest and S has intermediate mobility Naturally occurring mixtures of the various hemoglobin types are readily detectable

Genetic study of the family of the two children showed the maternal grandmother to be a carrier of the hemoglobin C trait and her two children heterozygotes for this element The children s father also harbored the gene for hemoglobin C Of five siblings one was normal two had the hemoglobin C trait and two were homozygotes (the patients studied) These findings support the postulate that pure

hemoglobin C disease results from mating of two persons each harboring the abnormal gene for hemoglobin C

Splenic Infarction Following Air Travel and Associated with Sickling Phenomenon The triad of splenic infarction sicklemia trait and high altitude flying has been previously reported Reduced oxygen tension associated with air travel has been considered a factor in precipitating sickle cell crises and incidence of sickling seemed to be directly proportional to altitude and duration of reduced oxygen tension in studies in actual flight conditions to altitudes of 15 000 ft However in low pressure chamber studies on Negro aviation cadets with sicklemia intravascular sickling was not found even at pressures simulating 10 000 ft Increased sickling developed in one man but he withstood lowered oxygen tension better than normal controls or sicklemia subjects intravascular sickling was relieved by oxygen

John P Doenges Ernest W Smith S P Wise III and R B Breitenbucher[3] (U S Army Hosp Fort Jackson S C) report the combination of sickle cell and C hemoglobin which is responsible for sickle cell hemoglobin C disease in two Negroes with splenic infarction after flying Sickle cells and hemoglobin C were found in the blood of both and target cells were present in the peripheral blood of one These findings suggest that the syndrome of infarction and intravascular sickling may occur not only in sickle cell trait but also in sickle cell hemoglobin C disease Similar cases in the future should be observed for presence of target cells Electrophoretic studies of hemoglobin of similar patients will undoubtedly be helpful

The military implications of the association of splenic infarction sickle cell phenomenon and flight seem important and it is equally important that genetic diagnosis be established If sickle cell trait alone is present in these occurrences of splenic infarction then approximately 7% of all Negroes face potential hazard in air travel However if both sickling factor and C hemoglobin are prerequisites the percentage would be substantially reduced

[Probably the essential combination for the syndrome is blood that will sickle and the presence of a spleen perhaps somewhat enlarged Patients with homozygous sicklemia are not likely to be aviators or to have intact spleens —Ed]

(3) 156 955 957 N 6 1954

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F g 60—P p r lect pho p tt f h moly t s of two p t ts (Courte y f S ge K et l Blood 9 10 3 1031 N mb 1954)

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[Further evidence at least for a histotoxic effect of cobalt and so possibly concerned with oxygen transport in tissues and related to the polycythemia producing action of cobalt —Ed.]

Decreased Red Cell Survival Associated with Liver Disease Use of Radioactive Sodium Chromate in Measurement of Red Cell Survival Although it has long been known that anemia is frequently present in chronic liver disease particularly in cirrhosis the etiology has been obscure Since the anemia is often macrocytic a deficiency in the antipernicious anemia factor has been suspected but this has been largely discredited because of lack of response to liver extract and because the bone marrow is rarely megaloblastic *In 1937 using a method detecting increased de*truction of red cells Watson reported seven cases of hemolytic anemia with cirrhosis among 135 patients with jaundice or hepatic disease Recently Chapman and Mollison using the Ashby technic found reduced red cell survival time in five cases of severe decompensated cirrhosis

Using the radioactive sodium chromate method to measure in vitro labeled red cell survival time Philip N Jones Irwin M Weinstein Richard H Ettinger and Richard B Capps[5] (Chicago) studied 19 patients with acute and chronic liver disease Various types of cirrhosis were present in 15 1 had acute infectious hepatitis 2 had chronic hepatitis and 1 had chronic biliary obstruction Shortened apparent half life survival time of patients labeled red cells was found in 8 patients and borderline values in 4 all of whom had cirrho is Only three with abnormal red cell survival times had anemia but all eight had erythroid hyperplasia of bone marrow Reticulocyte count and fecal urobilinogen determinations did not detect the degree of hemolysis present in these cases The frequent association of thrombocytopenia leukopenia and splenomegaly suggests that the hemolysis is due to a hypersplenism syndrome This might be secondary to portal hypertension which was proved in six of the eight abnormal cases either by demonstration of e ophageal varices on esophagoscopy or by direct venous pressure measurements at surgery

These findings indicate that the significance of hyperbilirubinemia in liver disease must be interpreted in the light of a possible hemolytic factor Even a relatively small increase in bilirubin in the presence of liver disease may re

(5) A M A A h I t Med 95 93 10 J uary 1955

Hemopoietic and Goitrogenic Effects of Cobaltous Chloride in Patients with Sickle Cell Anemia The most frequent side effect of cobalt therapy is gastric irritation which can be controlled with enteric coated tablets Less common but more serious effects are flushing rash tinnitus nerve deafness substernal pain and thrombocytosis Recently thyroid hyperplasia with hypofunction has been reported as a complication Ruth T Gross Joseph P Kriss and Theodore H Spaet[4] (Stanford Univ) describe the hemopoietic responses of four children with sickle cell anemia to cobaltous chloride and correlate them with thyroid dysfunction Enteric coated cobalt tablets were given orally (usually 2 3 mg /kg daily) and the children examined weekly or biweekly The following case illustrates the response

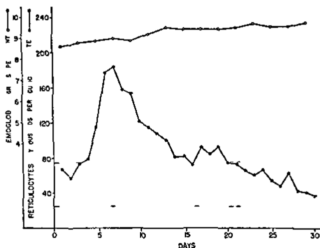
A Negro boy 6 had a hemoglobin value of 6 7 8 Gm for the 12 month period before treatment When cobalt 3 mg /kg daily was given the value rose to 10 Gm within two months Examination revealed a small goiter and radioiodine uptake dropped to 2%/24 hours Hemoglobin level dropped to 7 7 Gm during another month of cobalt therapy the goiter enlarged and symptoms of hypothyroidism developed Serum protein bound iodine was 1 µg /100 ml serum cholesterol 338 mg /100 ml and total serum lipids 1 610 mg /100 ml Thyroid biopsy showed marked hyperplasia Cobalt was discontinued and thyroid findings returned to normal within one month

Although initial hematologic response to cobalt is good prolongation of therapy leads to thyroid hypofunction and a decrease in hemoglobin concentration to pretreatment levels or less The drop in hemoglobin concentration could not be prevented even though the dose of cobalt was increased until it caused nausea and vomiting Goiters and hypothyroidism did not appear until the patients had been treated either for several months or with a very large dose The anemia which recurs with cobalt therapy may be secondary to hypothyroidism or other toxic action

The goitrogenic effect of cobalt alone or combined with other hematinics has been noted in premature infants and in a child with renal disease The mechanism of action may be inhibition of one of the essential enzymes involved in the synthesis of thyroxin Cobaltous chloride inhibits the tyrosine iodinase system in tissue homogenates and in surviving rat thyroid slices

(4) Ped tr c 15 284 290 March 1955

below 5 Gm /100 cc or showed the abnormalities of the red cell or granulocytic series characteristic of the bone marrows of vitamin B_{12} or folic acid deficiencies Hemolytic anemia was suggested by the persistently elevated reticulocyte levels increased concentration of red cell precursors in the bone marrow and heightened urobilinogen excretion Macrocytosis was not extreme correlated only



F g 61—Sp t ou se t locyt p t t w th h h l h l m d m ft h p t l t on d b t en E h poi t p ent th m f val s f fi p t t F mp b l t th th per entag et locyte l w e g i Upp d l w l m t f m l nd t d by hori ontal t pted l (Cou t y f J dl J H J Cl n I t 34 390 404 M h 1955)

roughly with the severity of anemia and has frequently been found in cirrhosis uncomplicated by anemia However it was felt that a patient with a hemoglobin level of less than 5 Gm or a mean corpuscular hemoglobin of more than 130 cu μ hould be suspect for folic acid deficiency

A reticulocyte peak developed at an average of seven days after hospital admission in five patients on alcoholic abstinence and a diet lacking in known hemopoietic factors (Fig 61) This suggests that alcoholic abstinence is followed by increased erythropoietic activity and that alcohol ingestion inhibits erythropoiesis to some extent in these

sult in significant elevation of serum bilirubin especially if hyperbilirubinemia is already present Increased hemolysis may occur in acute hepatitis also this would explain why higher levels of serum bilirubin are seen in acute hepatitis than in extrahepatic obstructive jaundice The findings also provide an explanation for the macrocytic anemia of chronic liver disease though other factors may be involved

The high incidence of gallstones in patients with abnormal apparent half life survival time of red cells may be the result of a hemolytic process transitory or intermittent It is also possible that gallstones perhaps because of an associated cholangitis may be an important contributing factor in chronic progressive liver disease

If the hyperbilirubinemia of liver disease is partly the result of increased red cell destruction then corticotropin and cortisone might produce their effect in liver disease (especially in lowering the serum bilirubin) by altering the hemolytic process rather than by acting on the liver

Anemia of Liver Disease Observations on its Mechanism are presented by James H Jandl[6] (Harvard Med School) Prior studies have shown no deficiency of vitamin B_1 and have suggested increased red cell destruction rather than metabolic defects inhibiting production in this anemia Red cell alteration with increased resistance to osmotic lysis have been described in association with biliary obstruction and infectious hepatitis but not in chronic liver disease

Studies were made on 10 men and 10 women aged 28-64 with chronic liver disease and various degrees of anemia but no evidence of any current or prior blood loss All were well documented chronic alcoholics with cirrhosis Diagnosis was verified in six by liver biopsy and in three at autopsy Observations were begun on the average of 6 days after hospital admission and continued for an average of 36 days Eleven improved clinically 4 showed no improvement and 5 died in hepatic coma Four of the 20 patients had hematologic findings consistent with folic acid deficiency complicating hepatic cirrhosis and the anemia responded to folic acid therapy None of the 16 patients with uncomplicated anemia of chronic liver disease had a hemoglobin level

(6) J Cl I est. 34 390 404 March 1955

below 5 Gm /100 cc or showed the abnormalities of the red cell or granulocytic series characteristic of the bone marrows of vitamin B_{12} or folic acid deficiencies Hemolytic anemia was suggested by the persistently elevated reticulocyte levels increased concentration of red cell precursors in the bone marrow and heightened urobilinogen excretion Macrocytosis was not extreme correlated only

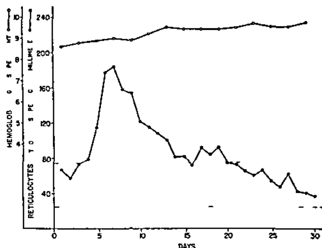


Fig 61 —Sponta eo ea t locyt p t en w th h h n lcoh l m d m aft h p t l t on d b t en Each poi t p esent th mea f l f fi p t t F mp b l t th th n pe entag t culocyt l w g d Uppe d l w l m t f orm l ind t d by hori ontal t rupt d l (C rt y f J dl J H J Cl I t 34 390 404 M h 1955)

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patients However studies of the survival of transfused normal red cells by the Ashby method in 15 patients indicated that an increased red cell destruction rate is the major factor in cirrhotic patients with subnormal hemoglobin levels and that the destruction rate correlates with the degree of anemia Thus the half survival time of red cells ranged from 5 to 51 days

Except for two patients whose plasmas contained low titers of cold agglutinins no indications of an immunologic basis for increased red cell destruction were found Survival was not enhanced by cortisone in two patients The average urobilinogen excretion was 257 3 mg /day—a distinct increase for an average hemoglobin level of 8 Gm / 100 cc The osmotic fragility of the red cells was normal except for a small proportion of abnormally resistant cells in many patients After sterile incubation for 24 hours the originally normal mechanical fragility of the red cells increased to an abnormal extent and there were abnormally great increases and decreases in osmotic fragility respectively of the most and of the least osmotically fragile red cells

Transfusions with Cr^{51} tagged autogenous red cells in a few patients resulted in a heavy concentration of radioactivity in the spleen and little activity in the liver This is in contrast to results with injected Cr^{51} tagged hemoglobin solutions and suggests that the spleen is the major site of red cell destruction in cirrhotic patients with anemia A hemolytic process which affects the survival of normal red cells as determined by the Ashby method is extracorpuscular by definition This however does not exclude an additional primary corpuscular defect The author points out that the exponential character of the survival curves of normal red cells is not inconsistent with a continuous fractional removal of red cells by a process which is intensive and localized rather than by a process which is diffuse and random

PERNICIOUS AND OTHER NUTRITIONAL MACROCYTIC ANEMIAS

Serum Vitamin B_1 Concentration in Pernicious Anemia Microbiologic determination of vitamin B_{12} in body fluids using Euglena gracilis var bacillaris was first described by Ross in 1950 Using the method of Hutner *et al* Ross showed that growth supporting activity of native serum is maximal when the diluted serum after being added to the medium is heated to 100 C for 15 minutes Values obtained before heating represent so called free vitamin B_{12}

SERUM VITAMIN B CONCENTRATIONS

Group	No. of Subjects	Total Vitamin B12	
		Range	Mean ± S D (μμg/ml)
Normal	20	292-856	532 ± 161
Pernicious anemia in relapse	33	0-85	39 ± 26
Pernicious anemia in remission	22	123 1,330	575 ± 337
Neurologic disease	14	195 760	439 ± 170
Achlorhydria (after histamine)	9	225 800	450 ± 234
Folic acid deficiency	12	148 557	307 ± 130
Hepatic cirrhosis	29	19[illegible] 2,200	714 ± 534
Miscellaneous	40	115 1,029	— —

S D = Standard deviation

The difference between total and free vitamin B_{12} was considered to indicate the amount of the vitamin loosely bound to serum protein Arnold A Lear John W Harris William B Castle and Eleanor M Fleming[7] (Harvard Med School) report recent results of microbiologic assays of serum in 179 subjects by a modified method

The values for total serum vitamin B_1 in several groups of patients are shown in the table Free (unbound) vitamin B_{12} was found in all samples from the 20 healthy persons and ranged from 27 to 104 μμg/ml Of 33 patients with pernicious anemia in relapse none showed any free vitamin B_1 Blood for the determinations made on 22 patients with pernicious anemia in remission was taken not less than four weeks after the last intramuscular

(7) J Lab. & Clin Med 44 715 722 November 1954

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normal persons and those from patients with pernicious anemia Whether this binding property is a function of a specific component (alpha globulin) of serum serving as the vitamin B_1 transport vehicle or is nonspecific is not firmly established That a specific vitamin B_1 binding or transport deficiency may exist has been suggested by Horrigan and Heinle in a case report of macrocytic anemia

Recent Studies of Intrinsic Factor and Utilization of Radioactive Vitamin B_1 are reviewed by Robert F Schilling[8] (Univ of Wisconsin) Berk *et al* showed that small oral doses of vitamin B_1 alone caused little or no reticulocyte response in pernicious anemia patients in hematologic relapse but the same dose given with neutralized normal human gastric juice was followed by a definite response In 1952 Welch *et al* reported that when pernicious anemia patients were given vitamin B_1 Co^{60} orally more radioactivity was demonstrated in the stools than in those of normal subjects i e 72 96% of the oral dose of 0 5 µg Fifty observations published and unpublished show that in 34 patients who received B_1 Co^{60} orally without added intrinsic factor 72 100% was excreted whereas in 27 observations on 23 of the same patients with added intrinsic factor only 25-66% was excreted

In 1953 Schilling described another method of demonstrating that intrinsic factor enhances absorption of orally administered vitamin B_1 Normal persons given 1 or 2 µg B_1 Co^{60} orally and two hours later 1 000 µg nonradioactive B_{12} (as a carrier) subcutaneously will excrete 3 25% of the orally administered radioactive material in the urine in 24 hours Under similar experimental conditions 17 pernicious patients in remission (or relapse) had a 24 hour excretion of radioactivity of 0 2 5% (table) With the same amount of B_1 Co^{60} given simultaneously with intrinsic factor the same patients had a sharp rise in radioactivity [with the solubility properties of vitamin B_1 —Ed]

A third technic was introduced by Glass and colleagues who measured radioactivity over the liver after giving B_{12} Co^{60} orally Gamma emission of Co^{60} can be studied with a directional scintillation counter Injected B_1 Co^{60} disap

(8) *Fed rat on P oc 13 769 775 S pt mbe 1954*

dose of vitamin B_{12} The 12 patients considered to have folic acid deficiency with macrocytic anemia and megaloblastic bone marrows had vitamin B_1 levels well above the relapse range for pernicious anemia and subsequently responded to folic acid therapy Among the 14 with neurologic evidence of posterolateral column disease but without typical pernicious anemia there were 5 with histamine fast achlorhydria Some of the nine with achlorhydria persisting after histamine had mild nondescript anemia

The 5 of 29 patients with hepatic cirrhosis and unusually high B_{12} levels each had other diseases and differed clinically in apparent severity of the liver disease as well as associated illnesses None had received vitamin B_1 Free B_1 levels ranged from 0 to 413 μμg /ml for the group as a whole The miscellaneous group of 40 contained patients with anemias associated with iron deficiency malnutrition myxedema hemolytic syndromes and various chronic diseases

Attempts to destroy the vitamin B_1 activity by alkalinization and heat succeeded in decreasing growth supporting activity of the serums by 48% (average) For normal serum and for that of patients with pernicious anemia in relapse to which vitamin B_{12} had been added the percentages were 39 and 34 These observations suggested that serum prevented complete degradation of its Euglena growth supporting property because vitamin B_{12} in saline so treated lost this property entirely

As a result of therapy sulfonamide derivatives may be present in serum in concentrations which can inhibit Euglena growth The inhibitory effect which may explain the apparently depressed vitamin B_1 levels in patients receiving this therapy may be abolished by para aminobenzoic acid added in vitro but not by pteroylglutamic acid or by the citrovorum factor

The studies indicate that serum contains a factor or factors which exert a binding effect on vitamin B_{12} and make it unavailable to support growth of E gracilis until this effect is destroyed by heating No difference in capacity to bind vitamin B_{12} was observed between serums from

normal persons and those from patients with pernicious anemia Whether this binding property is a function of a specific component (alpha globulin) of serum serving as the vitamin B_1 transport vehicle or is nonspecific is not firmly established That a specific vitamin B_1 binding or transport deficiency may exist has been suggested by Horrigan and Heinle in a case report of macrocytic anemia

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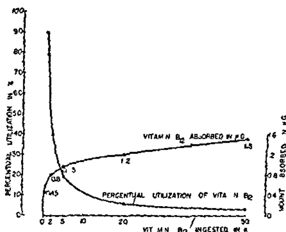
(8) Federation Proc 13 769 775 Septembe 1954

peared from the injection site in a few minutes and radioactivity reached a maximum in the liver five to seven days after injection It 0 5 μg $B_{12}Co^{60}$ injected parenterally results in an average hepatic radioactivity of 200 counts/

PER CENT OF URINARY RADIOACTIVITY AFTER ORAL B Co^{60}*

SUBJECTS	MAXIMUM	MINIMUM	AVERAGE
Control with gastric acid (5)	19 5	3 3	11 0
Achlorhydric without pernicious anemia (16)	20 3	4 6	11 4
Pernicious anemia without added intrinsic factor (17)	2 5	0	0 6
Pernicious anemia with added intrinsic factor (17)	15 0	3 1	8 0
Total gastrectomy without added intrinsic factor (4)	0 7	0	0.3

R dioact vity n the 4 h ur r n c llect is exp essed as p rce tage of the orally dm n te ed r d oa t v ty



F g 6 —A ge nte t l t l at on f t m B e m rm l bje t (Court sy of S h ll g R F Federat on Proc 13 769 775 S ptemb r 1954)

minute while an oral dose of 2 μg also results in an average hepatic radioactivity of 200 counts it is concluded that the patient absorbed 0 5 μg of the 2 μg oral dose this assumes that the ratio of hepatic to total body vitamin B_{12} is similar after oral and parenteral assimilation With this technic percentage absorption of an oral dose of vitamin B_1 decreases

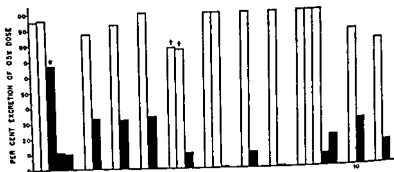
as the amount of vitamin B_{12} given orally is increased this is termed regression of percentual intestinal utiliza tion (Fig 62) Pernicious anemia patients demonstrate ra dioactivity over the hepatic area only when intrinsic factor is given with the radioactive vitamin

Intrinsic factor is water soluble nondialyzable will pass through a Berkefeld filter and is precipitated in a saturated solution of ammonium sulfate Freezing and thawing once or freeze drying will not destroy the activity Activity in human gastric juice is destroyed by boiling for 10 minutes regardless of presence or absence of vitamin B_{12} but an intrinsic factor vitamin B_{12} mixture prepared from hog gastric mucosa has been reported to be hemopoietic even after boiling Gastric juice will combine with vitamin B_{12} to render the vitamin unavailable for utilization by certain microbes but many preparations which bind vitamin B_{12} have little or no intrinsic factor activity Boiled gastric juice still binds vitamin B_1 however active intrinsic fac tor preparations also bind some vitamin and there is no evidence that intrinsic factor does not bind vitamin B_{12} It has been suggested that intrinsic factor prevents bacterial utilization of intestinal vitamin B_1 thus enabling the pa tient to absorb more vitamin but this theory no longer is attractive Increasing the oral dose of the vitamin (with out intrinsic factor) to levels beyond what might be re quired to satisfy bacterial demand does not result in more than slight increases in total $B_{1.}$ absorption

Wijmenga and colleagues isolated an electrophoretically homogeneous red protein from hog gastric mucosa with a high vitamin B_{12} binding capacity [The color was due to pre ence of the bound vitamin but the preparation was without activity as intrinsic factor —Ed] Latner and Ung ley reported that a concentrated preparation of intrinsic factor (active in 2 mg dose level) was a mucoprotein judg ing from its hexose content lysine histidine and tyrosine were lacking Glass had earlier associated intrinsic factor with gastric mucoprotein but the daily quantity of muco protein used for demonstration of intrinsic factor activity was 50 200 mg As little as 10 ml lyophilized human gastric juice will be moderately active Since 10 ml gastric juice

contains only about 15 mg nondialyzable solids there is some reason to doubt Glass s concept It appears that intrinsic factor is a mucoprotein but not all mucoprotein in gastric juice is intrinsic factor Nitrogen content of Latner s most concentrated intrinsic factor preparations is about 9% and molecular weight has been estimated at 17,000

Absorption of Radioactive Vitamin B_{12} after Total Gastrectomy Relation to Macrocytic Anemia and to Site of Origin of Castle s Intrinsic Factor Since vitamin B_{12} contains cobalt in its molecule radioactive vitamin B_{12} can



F g 63—Fec l ex r t n of Co^{60} l beled t m n B fte t tal g t ectomy Du ng *H k te ol mn* 0 5 μg v tam n B lon d *bla k* w th ga t c ju e wh h m y ex th s te t a re d hea devel p d sh rtly after d w s g v mpl t d t pla th h gh xc t on †D ring these t t stool ollection w s h t k g ontra t a cl ded b au r lt of t t w th g t J i n New E gla d J Med 251 161 168 J ly 29 (C u te y f H l ted J A *t al* New E gla d J Med 251 161 168 J ly 29 1954)

be produced by use of Co^{60} in its synthesis This can be detected in the feces in minute amounts by a sensitive scintillation counter owing to intense gamma emission of isotopic cobalt as first shown by Heinle Welch *et al* Using this method James A Halsted Marvin Gasster and Ernst J Drenick[9] (Los Angeles) found that 11 normal persons excreted on the average 33% of 0 5 μg orally administered radioactive vitamin B_{12} Three patients with idiopathic achlorhydria excreted an average of 34% of a similar dose Seven patients with pernicious anemia excreted an average of 93% in 10 tests but when a source of intrinsic factor

(9) N w Engl nd J Med 251 161 168 J ly 29 1954

(gastric juice) was given with the test dose in four patients fecal excretion decreased to 38% Eleven patients who had had total gastrectomy excreted an average of 87% in 16 tests When intrinsic factor was given with the test dose an average of only 20% was excreted in 14 tests (Fig 63) No definite correlation between degree of fecal excretion and amount of gastric juice used could be determined

Site of secretion of intrinsic factor has been the subject of controversy That it is limited to the stomach in man has been suggested by experiments in which juice obtained from the *duodenum was without intrinsic factor activity* also Paulson and associates found no intrinsic factor in duodenal juice after total gastrectomy Although desiccated normal human duodenum had some intrinsic factor activity passive adsorption or active absorption of gastric intrinsic factor by tissue could not be excluded

From these and the present observations it appears that patients with total gastrectomy do not absorb vitamin B_{12} from dietary sources but do not invariably have anemia Four factors may explain this paradox (1) Not many patients survive operation long enough for macrocytic anemia to develop (2) Clinical evidence suggests that vitamin B_{12} may be stored in the liver for long periods The human requirement *is not over 1 µg/day or less than 0 5 mg/year* Thus liver stores in the patient who has had a total gastrectomy may be sufficient for several years Review of 12 cases of macrocytic anemia of pernicious anemia type among 46 patients with total gastrectomy showed that the anemia appeared four years or more after surgery in 9 and six months after cessation of liver therapy in 1 (3) It is sometimes technically difficult to excise the cardiac end of the stomach above the esophagocardiac junction and 1 or 2 cm *of cardia may be left behind although these cases are* reported as total gastrectomies Since the cardia is an active site of secretion of intrinsic factor a small segment left in situ might secrete enough for normal use of vitamin B_{12} from the diet (4) Probably the most important reason that only a few patients who survive total gastrectomy manifest a macrocytic anemia is that antianemic preparations are so widely prescribed Even if the surgeon does not advise this

medication most patients receive it from their own physicians Of 11 patients with total gastrectomy in this series none had macrocytic anemia but 9 had received prophylactic therapy

Hematologic Alterations after Total Gastrectomy Evolutionary Sequences over a Decade Moses Paulson and John

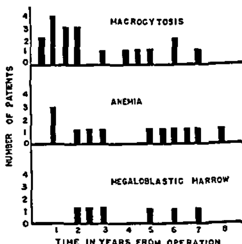


Fig 64—E l t n f h matol g c h ges towa d macrocytic megal bl st c an m a in 7 p t ts w th tot l g t t my (C rtesy of P l on M a d H rvey J C J A M A 156 1556 1560 Dec 25 1954)

Collins Harvey[1] (Johns Hopkins Univ) report observations on 21 men and 6 women aged 35-65 10 years after gastrectomy Frequent peripheral blood examinations were made and bone marrow studies were done postoperatively and about every six months Gastric analyses of 23 patients before operation showed 19 with free acid and 4 with persistent achlorhydria

Total gastrectomy was performed in all Pathologic diagnoses were carcinoma in 23 lymphosarcoma 2 benign ulcer, 1 and chronic gastritis 1 All patients had iron deficiency anemia two or three months postoperatively from slow blood loss from eroded and inflamed areas in the

(1) J A M A 156 1556 1560 Dec 25 1954

lower esophagus and jejunum It was controlled by oral ferrous gluconate or sulfate

In 19 patients macrocytosis developed six months to seven years postoperatively (Fig 64) with macrocytic anemia following in one to two years and megaloblastic bone marrow soon after One patient also had folic acid deficiency *established by further response to folic acid orally after* partial response to vitamin B_{12} parenterally The macrocytic anemia responded to vitamin B_1 parenterally used in almost all cases One patient was given 0 5 µg vitamin B_{12} orally labeled with cobalt-60 *87%* was recovered in the stool In normal patients only 10–40% was recovered The studies confirm other evidence that vitamin B_{12} is not absorbed by the stomach alone and cannot be absorbed efficiently in the intestines without normal gastric juice

Delay in development of macrocytic anemia is unexplained [See preceding article for possible explanations — Ed] The data suggest that the duodenum and jejunum produce either no intrinsic factor or amounts insufficient to prevent its development

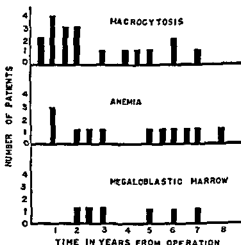
Stomach in Pernicious Anemia Cytologic Study reported by Barbara W Massey and Cyrus E Rubin[2] (Univ of Chicago) was stimulated by a false positive interpretation in a cytologic examination for detection of gastric malignancy in a patient with treated pernicious anemia The cells were much larger than normal varied in size and had heavy nuclear membranes cells of this type had been seen before only in stomachs with malignant disease Smears from the stomachs of 21 patients with treated pernicious anemia in complete hematologic remission were examined Length of treatment ranged from 6 months to 22 years (average 7 years)

Most gastric columnar cells were not unusual and had normal nuclei (Fig 65) However all 21 patients had a few groups of abnormal columnar cells of apparently specific type designated P A cells (Fig 66) Average area was 6 2 units twice that for normal cells When control and P A cells were taken from the same patient average difference between mean sizes of normal and abnormal cells

( ) Am J M Sc 2 7 481-492 M y 1954

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Hematologic Alterations after Total Gastrectomy Evolutionary Sequences over a Decade Moses Paulson and John



F g 64—E ol t on f hematol gic ch g s t wa d m crocyt c megal blast c n m a in 7 pat ts w th t t l ga tr t my (C tesy f P l on M d Harvey J C J A M A 156 1556 1560 Dec 25 1954)

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(1) J.A.M.A 156 1556-1560 Dec. 25 1954

find characteristic P A cells Multiple smears from mucosal scrapings of two stomachs resected for polyps revealed no consistent localization of P A cells and the polyps showed no cellular changes comparable to those in the smears

Goblet cells and slender elongated cells with small central pyknotic nuclei were frequently seen A third heterogeneous group of cells between normal and P A cells showed variable nuclear enlargement and atypia not pronounced enough to be characteristic of pernicious anemia

Studies on untreated pernicious anemia showed gastric P A cells indistinguishable from those seen in other cases after years of therapy Investigation of a larger series is necessary to determine whether this cell is pathognomonic of pernicious anemia if so diagnosis could be established despite previous specific therapy

[This report should be compared with that of Graham and Rheault (1954 55 YEAR BOOK p 252) which demonstrated macrocytosis and J Lab & Clin Med. 43 235 February 1954 and nuclear abnormalities of squamous and columnar cells in gastric aspirations in pernicious anemia patients that were reversible by vitamin B therapy—Ed]

Pernicious Anemia and Cancer of Stomach Preliminary Report Johannes Mosbech[3] (Copenhagen) assessed the frequency of gastric cancer among relatives of patients with pernicious anemia and among relatives of a control group of healthy persons of similar sex and age Clinical observations and systematic roentgenographic studies in patients with pernicious anemia (without gastric symptoms) indicated that gastric carcinoma is more common in patients with pernicious anemia than in other persons of similar age Patients with pernicious anemia also have about three times the usual expected mortality from gastric carcinoma

Carcinogenic action of liver preparations has been suggested as an explanation for increased stomach cancer in pernicious anemia but the hypothesis lacks clinical and experimental support There is evidence that inherited factors are present in pernicious anemia and recent findings indicate that gastric carcinoma also has hereditary features If common inheritance can explain why patients with pernicious anemia are more susceptible to cancer of the stomach

(3) A ta m d sc d 148 309 315 1954

was 3 1 (standard error 0 25) the same ratio was obtained for the whole series (1 131 cells) including normal control cells from nonpernicious anemia patients Probability of chance occurrence of these abnormal cells in pernicious anemia is less than 5 in 10 000

In the large abnormal cells the nuclear membrane often



F g 65 (l ft) —N mal g t c l mn ll ×750
F g 66 (gbt) —P A ll fte th e y t tm t ×750
Cou t y f Ma s y B W a d R b C E Am J M S 7 481 49 May 1954)

appears creased or folded In the majority small aggregates of chromatin stand out on the relatively empty background of the nucleus Sometimes the cytoplasm appears abnormally vacuolated and granular Perinuclear halos or half moon shaped vacuoles may be seen (Fig 66)

Large columnar cells closely simulating malignancy were also found in several cases (active P A cells) The nuclei were twice normal size nuclear membranes were irregular and nucleoli were large red and refractile Cell outlines were definitely columnar or at times squamous like The nuclear cytoplasmic ratio was not disturbed and the hyper chromatism and size variation were of lesser degree than in carcinoma

In three cases repeat cytologic studies were necessary to

eral blood and with normoblastic bone marrow and two cases in which peripheral neuropathy was associated with histamine fast achlorhydria and a normal peripheral blood count In one minimal changes in the sternal marrow sug gested pernicious anemia

CASE 1—Woman 54 had unsteadiness in walking tingling of hands and feet and intermittent numbness around and below the waist She had histamine fast achlorhydria hemoglobin 77% red cells 4 000 000 mean corpuscular volume 87 μ^3 white cells 5 000 (neutrophils 32%) and reduced platelets Sternal puncture showed increase of proerythroblasts but no excess of early or intermediate normoblasts no megaloblasts or giant metamyelocytes Remission of neurologic symptoms followed treatment with vitamins B_1 and C iron and exercise but severe relapse a year later was accompanied by changes in peripheral blood and marrow Color index was 1 6 hemoglobin 67% mean corpuscular volume 129 μ^3 red cells 2,130 000 macrocytosis and anisocytosis and white cells 6 100 (neutrophils 53%) Marrow showed well marked megaloblastic erythro poieses and numerous giant metamyelocytes Blood picture improved rapidly on vitamin B_1 and the anemia remained well controlled until death from complications (urinary infection and bed sores) of extensive and by then irreversible cord disease six months later

In Case 3 a three year remission followed therapy with only 350 µg vitamin B_{12} in a woman 28 with mild neu ropathy mainly peripheral Then with relapse changes typi cal of pernicious anemia appeared in blood and bone mar row these responded well to liver therapy In three other patients with neuropathy who received adequate vitamin B_1 anemia did not develop neurologic signs did not advance and to a certain extent regressed In two of them the marrow contained giant metamyelocytes which in one disappeared on vitamin B_1 therapy These cells may be one of the earliest indications of pernicious anemia and were reported by Wil on as the only marrow abnormality in a similar case Two patients had peripheral neuropathy associated with histamine fast achlorhydria and a normal peripheral blood count In one of them minimal changes in sternal marrow also suggested beginning pernicious anemia

Patients with histamine fast achlorhydria are variably liable to develop manifestations of vitamin B_{12} deficiency but relative susceptibility of peripheral nerves spinal cord and marrow is unpredictable Early treatment of neurologic

the disease would be expected particularly often among relatives of these patients

Cancer of the stomach was the cause of death in 108 of 2 881 relatives of 234 pernicious anemia patients and in only 33 of 2 956 relatives of 225 controls Cancer of the esophagus and of other sites was also more common in the pernicious anemia series but the differences between groups were much less Deaths from gastric cancer were more frequent among relatives of pernicious anemia patients than might be expected in the general population whereas in the controls they were fewer Both deviations from computed mortality were significant

No exogenous causes of gastric carcinoma were found in the pernicious anemia series Hence it is reasonable to explain excess mortality from gastric cancer among patients with pernicious anemia and their relatives as a hereditary phenomenon due to a common predisposition to both pernicious anemia and stomach cancer A constitutional defect of the gastric mucosa in these persons causes achlorhydria and reduced resistance The nature and intensity of various exogenous effects probably determine whether the predisposed individuals have pernicious anemia gastric carcinoma or both

[This confirms previous work of others Gastric cancer detection studie if not too laborious or costly should be especially useful in patients with achylia gastrica —Ed]

Subacute Combined Degeneration of Cord and Achlorhydric Peripheral Neuropathies without Anemia Although manifest pernicious anemia and subacute combined degeneration usually coexist either may precede the other for a variable time Signs of peripheral neuropathy may also be harbingers of cord degeneration and may antedate appearance of pernicious anemia Marrow studies are helpful in diagnosis but characteristic megaloblastic dysplasia may be entirely absent when the peripheral blood count is normal If the patient is untreated changes typical of pernicious anemia may later develop and the neurologic condition rapidly deteriorate

Eric C O Jewesbury[4] reports five cases of subacute combined degeneration with insignificant changes in the periph

(4) Lancet 2 307 312 Aug 14 1954

eral blood and with normoblastic bone marrow and two cases in which peripheral neuropathy was associated with histamine fast achlorhydria and a normal peripheral blood count In one minimal changes in the sternal marrow suggested pernicious anemia

CASE 1—Woman 54 had unsteadiness in walking tingling of hands and feet and intermittent numbness around and below the waist She had histamine fast achlorhydria hemoglobin 77% red cells 4 000 000 mean corpuscular volume 87 μ^3 white cells 5 000 (neutrophils 32%) and reduced platelets Sternal puncture showed increase of proerythroblasts but no excess of early or intermediate normoblasts no megaloblasts or giant metamyelocytes Remission of neurologic symptoms followed treatment with vitamins B_1 and C iron and exercise but severe relapse a year later was accompanied by changes in peripheral blood and marrow Color index was 1 6 hemoglobin 67% mean corpuscular volume 129 μ^3 red cells 2,130 000 macrocytosis and anisocytosis and white cells 6 100 (neutrophils 53%) Marrow showed well marked megaloblastic erythropoieses and numerous giant metamyelocytes Blood picture improved rapidly on vitamin B_1 and the anemia remained well controlled until death from complications (urinary infection and bed sores) of extensive and by then irreversible cord disease six months later

In Case 3 a three year remission followed therapy with only 350 µg vitamin B_{12} in a woman 28 with mild neuropathy mainly peripheral Then with relapse changes typical of pernicious anemia appeared in blood and bone marrow these responded well to liver therapy In three other patients with neuropathy who received adequate vitamin B_1 anemia did not develop neurologic signs did not advance and to a certain extent regressed In two of them the marrow contained giant metamyelocytes which in one disappeared on vitamin B_1 therapy These cells may be one of the earliest indications of pernicious anemia and were reported by Wilson as the only marrow abnormality in a similar case Two patients had peripheral neuropathy associated with histamine fast achlorhydria and a normal peripheral blood count In one of them minimal changes in sternal marrow also suggested beginning pernicious anemia

Patients with histamine fast achlorhydria are variably liable to develop manifestations of vitamin B_{12} deficiency but relative susceptibility of peripheral nerves spinal cord and marrow is unpredictable Early treatment of neurologic

manifestations and prolonged observation are essential in these cases Although always suspect some peripheral neuropathies with histamine fast achlorhydria without anemia are due to causes other than vitamin B_{12} deficiency [but this cannot be known for a certainty unless a normal serum vitamin B_{12} level is found before vitamin B_1 therapy is given —Ed]

The terms pernicious anemia and subacute combined degeneration of the cord should be dropped in favor of vitamin B_{12} deficiency which may be qualified by adding megaloblastic anemia and/or neuropathy of whatever type is present

[This is a valuable account of failure to appreciate what the author so appropriately emphasizes that the manifestations of vitamin B deficiency appear variously and early or late as hematologic neurologic or gastrointestinal The neurologic manifestations of pernicious anemia are *not* the result of the anemia but of the vitamin B_1 deficiency a fact that can now be determined by microbial analysis of the serum

In view of the current tendency of the medical profession to prescribe vitamins for so many patients for whom they are of no demonstrable value it is unfortunate to miss opportunities where just one vitamin would be so specifically useful Presumably because the hematologist found "no evidence of pernicious anemia in Case 3 although vitamins B and C and an iron mixture were given vitamin B was not Is a therapeutic trial of vitamin B less justifiable than the unhallowed use of other vitamins? Actually the blood picture is probably never completely normal in such patients Thus in Case 3 had the blood picture been viewed with suspicion because of the neurologic manifestations and achlorhydria it would have been noted to be entirely consistent with early pernicious anemia Thus mild normocytic anemia and granulocytopenia together with thrombocytopenia were found With so little anemia the bone marrow would not have been expected to be strikingly abnormal and it was not

The early recognition of the neurologic as opposed to the hematologic manifestations of vitamin B deficiency is much more important because the former soon become to a certain extent irreversible It cannot be said too often that persistent symmetrical paresthesias in hands and/or feet with or without other findings mean vitamin B deficiency until proved to be due to other causes At any rate folic acid was not given in Case 3 in addition to the other useless vitamins and so was avoided the additional iatrogenic effect as Conley has emphasized of further obscuring the hematologic picture while enhancing the neurologic damage —Ed]

Long Term Evaluation of Vitamin B_1 in Treatment of Pernicious Anemia 1 Incidental Report on Use of Combined Oral Therapy with Vitamin B_1 and Folic Acid is presented by Steven O Schwartz Irving A Friedman and Helen L Gant[5] (Cook County Hosp) Clinical hematologic

(5) J A M A 157 2 9 231 J n 15 1955

and neurologic evaluations were made of parenteral therapy with vitamin B_1 given for four years to 32 patients with pernicious anemia and compared with results of liver extract therapy in 34 patients in the same period Of those receiving liver extract with monthly injections of 30 units *only three had slight recurrence of paresthesias but of* those treated with 30 µg vitamin B_{12} monthly four had neurologic relapses predominantly of decreased vibration sense reversible with increased vitamin B_{12} or adequate liver therapy

Of 36 patients treated daily with 25 µg vitamin B_1 *and 1 67 mg folic acid orally 1 had hematologic relapse* after 19 months treatment 9 had neurologic relapse within 15 36 months 1 had neurologic and hematologic relapse after 19 months and 3 had glossitis and weight loss after 19-49 months

The authors conclude that parenterally administered vitamin B_1 is adequate substitute for liver in sustaining pernicious anemia patients hematologically and neurologically provided adequate doses at frequent intervals are used Rapid excretion of vitamin B_1 and diminishing effect between doses were considered causes of neurologic relapses for they could be corrected with more frequent doses *Possible solutions for these objections are to (1)* give small doses at frequent intervals (2) give moderately large doses at infrequent intervals and (3) find a menstruum that would cause slower absorption of the injected vitamin After sustained intensive treatment there may be tissue saturation and storage (depletion of which may take considerable *time) permitting maintenance on smaller doses for* some time The relapse rate observed in these studies suggests that oral vitamin B_1 and folic acid therapy may be grossly inadequate hematologically neurologically and clinically

[Agreed that such oral therapy is potentially inadequate The risk may well be increased by the combination of vitamin B with folic acid of which the former is poorly the latter readily absorbed. Our experience does not however suggest that when given by injection even as little as 15 µg vitamin B once a month is inadequate for clinical hematologic and neurologic maintenance over months and years Nevertheless because half of our patients on 15 µg /month were found to have serum

vitamin B_1 levels of less than 100 $\mu\mu g$/cc the dose of vitamin B was increased to 30 μg injected once a month with the result that all serum vitamin B levels became normal In a few patients the hemoglobin levels also rose slightly Subsequent addition of 5 mg folic acid orally daily depressed the average serum vitamin B_1 levels somewhat but not to as low as 100 $\mu\mu g$/cc —Ed]

Treatment of Pernicious Anemia with Oral Vitamin B_{12} without Known Source of Intrinsic Factor produced satis factory hematologic response in 15 patients with megalo blastic anemia in relapse as reported by J N M Chalmers and Zaida M Hall[6] (St George s Hosp and Med School London) *Seven received single oral doses of 2 000 9 000* µg vitamin B_{12} which yielded hematologic responses sim ilar to those obtained by a single intramuscular injection of 20 100 µg Daily doses of 50 µg vitamin B_{12} taken orally when fasting caused significant hematologic responses in five patients Less satisfactory response was obtained in one patient when the same dose was taken with food In two the surface agent tween® 20 did not appear to be of value in aiding absorption of vitamin B_{12} One patient with pernicious anemia in relapse was initially treated and maintained in remission for over 18 months on a daily oral dose of 50 µg taken on retiring

The uniformly good results obtained with the daily oral doses of vitamin B_{12} could be related to strict fasting There are several possible reasons for this In the fasting state there is greater opportunity for the vitamin to come into contact with the intestinal mucosa Vitamin B_{12} may be destroyed by digestive secretions unless protected by intrinsic factor [doubtful —Ed] if so the small quantity of secretion in the fasting state may not destroy all the dose If intrinsic factor prevents utilization of vitamin B_1 by bacteria temporary alteration in bacterial flora in the fasting state may allow the vitamin to be absorbed The responses may have been obtained because patients with histamine fast achlorhydria were still secreting a small amount of intrinsic factor

Intramuscular preparations are preferable to and more convenient than oral for routine use but these cases dem onstrate that without intrinsic factor vitamin B_1 given

(6) B M J 1 1179 1181 May 22 1954

orally can be utilized when taken by fasting patients and that clinical and hematologic remission can be obtained

[In other words oral therapy of pernicious anemia with vitamin B is possible but is a *tour de force* that need not be exhibited to the public —Ed.]

Response of Megaloblastic Anemia of Pregnancy to Vitamin B_1 In recent years many conflicting reports have appeared on the effectiveness of vitamin B_1 in megaloblastic anemia of pregnancy It has also been suggested that cases responding to vitamin B_1 are actually cases of non tropical sprue In view of this H C Moore E W Lillie and P B B Gatenby[7] (Dublin) present 17 cases in which vitamin B_{12} was used Fat balance tests were done in six

METHOD —The usual hematologic studies were done The peripheral blood smear was not of great value since macrocytosis anisocytosis and poikilocytosis are much less marked than in true pernicious anemia In all cases diagnosis was confirmed by sternal marrow biopsy All patients were given vitamin B_1 intramuscularly in varying doses One received 20 µg daily 10 were given 100 µg daily for four days then 40 or 50 µg daily for variable periods 6 received 1 000 µg daily for five days Six also received iron therapy but in the others iron was withheld to obtain an uncomplicated reticulocyte response Folic acid (20 mg daily) was given orally to all patients not exhibiting a reticulocyte response to vitamin B_{12} in 8-10 days Fecal fat analyses were done on a four day total specimen with the patient receiving a diet containing 70 Gm fat and 70 Gm protein daily

Of the 17 patients 13 showed a reticulocyte response and hematologic improvement Vitamin B_{12} failed to produce a reticulocyte response in four two of whom received as much as 5 000 µg These four later responded to folic acid The bone marrow required at least three weeks for recovery Since the bone marrow in most patients treated with folic acid reverts to normal more quickly than in the present series of vitamin B_1-treated patients it was felt that the delay might be due to folic acid deficiency In four patients responding to vitamin B_1 folic acid failed to produce a second reticulocyte rise

There are therefore two groups of megaloblastic anemia of pregnancy depending on the response to vitamin B_1 and not all cases can be regarded as folic acid deficiency

(7) Irish J M S pp 106 116 March 1955

anemias Fat balance studies revealed no evidence of occult steatorrhea

[It is unfortunate that the therapeutic trials of parenteral administration of vitamin B_{12} employed such relatively large doses as 20 μg a day (instead of 1 5) because some mass action effect might be induced on a partial though limiting deficiency of folic acid However we agree entirely with the authors conclusion that two different kinds of deficiency may occur in the pernicious anemia of pregnancy vitamin B as well as folic acid —Ed]

Relationship of Vitamin B_1 and Folic Acid in Megaloblastic Anemias is discussed by H O Nieweg J G Faber J A de Vries and W F Stenfert Kroese[8] (Groningen The Netherlands) Substances used therapeutically in megaloblastic anemia include (1) folic acid factors—pteroylglutamic acid citrovorum factor (folinic acid) and their conjugates (2) vitamin B_{12} factors including the cobalamins and (3) nucleic acid constituents—uracil thymine and thymidine Vitamin B_1 and folic acid are *clinically most important* One group of megaloblastic anemias in which neurologic disorders may occur reacts to vitamin B_1 another group is refractory to B_{12} therapy but reacts to folic acid Comparison of B_1 levels in serums of these groups using Lactobacillus leichmannii A T C C strain 313 showed that in the first group represented principally by addisonian pernicious anemia B_1 content is low *In the second* group of which Wills tropical anemia is the classic *example vitamin* B_1 *values are normal or above* and folic acid activity of the blood for Streptococcus faecalis is below normal In pernicious anemia results of folic acid assay were variable In nearly half the cases values were low Following an injection of vitamin B_1 folic acid activity fell rapidly sometimes within two hours When the study was continued 72 hours or more a subsequent rise was noted

Available data on patients with addisonian pernicious anemia indicate that vitamin B_1 causes increased utilization of folic acid in the bone marrow and that it has either a direct or indirect influence on storage of folic acid in the liver Microbiologic studies indicate that folic acid and B_{12} are related to nucleic acid synthesis which is disturbed in megaloblastic anemia Two types of nucleic acid may be distinguished—desoxyribose (DNA) and ribose (RNA)

(8) J Lab & Cli Med 44 118 132 J ly 1954

DNA contains the pyrimidine bases thymine and cytosine RNA cytosine and uracil RNA occurs in the cytoplasm and nucleolus of the cell whereas DNA is found only in the nucleus and is considered an essential constituent of chromosomes When lack of vitamin B_{12} or folic acid slows DNA production tissues characterized by intensive DNA production are noticeably disturbed i e tissues with frequent mitoses such as bone marrow and the gastrointestinal tract In the adult the nerve cell does not show cell division and

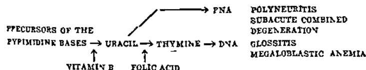


Fig 67.—I t ct on f f lic c d d vitamin B c d g t m difi t on f th theory of J ke B oq t d Stokst d (Court y of N ew g H O et l J Lab & Cl n M d. 44 118 132 J ly 1954)

DNA turnover is low but RNA content is high In the nerve cell intensive protein synthesis is required to maintain integrity of the axon whose estimated total ma s is about 1 000 times the cytoplasmic mass of the perikaryon in some neurons Continuous centrifugal flow of cytoplasmic material along the axon has been demonstrated It is not surprising that the neurologic manifestations accompanying B_1 deficiency are found in nerve cells with the longest axons where RNA protein synthesis is most active

The authors present the following explanation of the interaction of folic acid and vitamin B_1 (Fig 67) Vitamin B_1 deficiency may lead to both nervous system lesions and hematologic disorders lack of folic acid however causes anemia but the nervous system remains intact This is perhaps because vitamin B_1 is necessary for synthesis of both DNA and RNA It is essential for production of the pyrimidine ring of uracil and cytosine while folic acid is responsible for formation of thymine (5 methyluracil) from uracil and so eventually for RNA Thus it is clear why in folic acid deficiency vitamin B_1 is ineffective In B_1 deficiency folic acid may correct the hematologic manifestations because most of the limited supply of pyrimidine

bases is used for thymine formation Pyrimidine bases available for RNA synthesis will decrease even more which may lead to more rapid possibly explosive development of nervous system lesions As long as sufficient vitamin B_{12} is available for pyrimidine synthesis even large amounts of folic acid will not cause nervous system damage Inability of folic acid to produce nervous system lesions in iron deficiency or pernicious anemia patients given sufficient vitamin B_1 has been adequately demonstrated It is also easy to see why both uracil and thymine may be effective in pernicious anemia whereas uracil had no effect on a patient with megaloblastic anemia of pregnancy who responded to thymine In a later pregnancy the patient again had anemia refractory to B_1 and folic acid proved effective Although this purely nutritional hypothesis explains the clinical facts the authors stress that it is merely speculative

Clinical Studies with Citrovorum Factor in Megaloblastic Anemia in six patients are described by R Janet Watson Herbert C Lichtman Jacqueline Messite Rose Ruth Ellison Harold Conrad and Vitor Ginsberg[9] (State Univ of New York) In 1948 a substance called citrovorum factor (CF) essential for growth of Leuconostoc citrovorum 8081 was discovered in liver extract and in yeast Its microbiologic and chemical properties are distinct from vitamin B_1 and pteroylglutamic acid (PGA) but its similarity to the latter immediately suggested a close metabolic relation Experimental studies indicate that CF is a biologically active derivative of PGA and is perhaps the compound to which PGA must be changed in vivo to exert its effect on metabolic processes Inter relationships between vitamin B_1 PGA and CF have not been clarified but it appears that viamin B_1 compounds (cobalamins) and PGA CF activity substances (pteroylglutamates) participate in nucelo protein synthesis and are critically concerned with metabolic processes which if disturbed can alter the integrity of all body tissues [See preceding article by Nieweg *et al* —Ed]

Therapy with 5 mg CF daily by mouth for four months given to a patient with addisonian pernicious anemia re

(9) Am J M d 17 17 8 J ly 1954

sulted in acute combined systemic disease which cleared promptly on changing to parenteral admini tration of vita min B_1 Use of CF (like PGA) is undoubtedly contraindi cated in this disease Possibly the hematologic response to CF or PGA may further deplete the already sparse body stores of vitamin B_1 to a critically low level

Five patients with nutritional megaloblastic anemia had

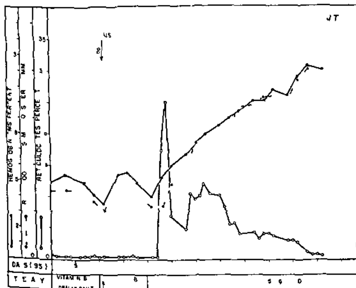


Fig 68—Labo i y fi d g d b d (C t y f W t R J Am J M d 17 17 28 J ly 1954)

hematologic remissions after therapy with CF One re ceived it orally the others by injection Four had previously failed to improve while receiving vitamin B_1

Man 62 with hypertension had progressive dyspnea orthopnea and weakness for one month Diet had been inadequate for many months Hepatomegaly plenomegaly icterus and edema were ab sent Vibratory and position senses were intact and deep reflexes were active Hemoglobin was 4 9 Gm red blood cell count 1 420 000 hematocrit 13% mean corpuscular volume 91 5 μ^3 mean corpuscular hemoglobin concentration 37 6% mean corpuscular hemoglobin 34 5 μμg reticulocytes 0 8% icterus index 7 5 units

leukocytes 2 400 with normal differential count. Bone marrow was megaloblastic Free acid was present in gastric secretions 30 minutes after histamine injection Vitamin B_{12} 50 µg /day orally for 10 days failed to elicit reticulocyte response hemoglobin and red cell values were unchanged Intramuscular injection of 90 µg vitamin B_{12} and one blood transfusion also had no effect. On the seventh day of treatment with 1 5 mg CF intramuscularly daily reticulocytes reached 25% and red blood cell count began to rise On discharge 37 days after first injection of CF hematologic findings were essentially normal (Fig 68)

Two patients apparently had dual deficiencies of vitamin B_{12} and CF In one with addisonian pernicious anemia (vitamin B_{12} deficiency) a superimposed deficiency of CF developed The other with cirrhosis of the liver and nutritional megaloblastic anemia had good hematologic remission initially when given vitamin B_{12} but later relapsed while receiving 45 µg vitamin B_{12} by injection each month and responded only to CF given intramuscularly

In megaloblastic anemias with associated gastric achlorhydria vitamin B_{12} is the drug of choice [and should always be given a trial before other therapy —Ed] In nutritional megaloblastic anemia when hydrochloric acid is found in the gastric juice treatment with citrovorum factor or pteroylglutamic acid is indicated However certain patients with achlorhydria and megaloblastic anemia may not have vitamin B_{12} deficiency but rather require citrovorum factor or pteroylglutamic acid

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HYPOCHROMIC ANEMIA

Studies in Iron Transportation and Metabolism IX Excretion of Iron as Measured by Isotope Technic Reubenia Dubach Carl V Moore and Sheila Callender[1] (Washington Univ) used Fe^{55} and Fe^{59} to study iron excretion and metabolism This technic permits differentiation of excreted iron from iron present because of contamination or lack of absorption from food The isotope was given intravenously except in two subjects who had taken it orally long enough before the study period so that only the isotope derived

(1) J Lab & Clin Med 45 599 615 Apr l 1955

from previously absorbed iron could have been excreted

Fecal excretion studies were done on five normal subjects three patients with hypochromic anemia and two with hemolytic anemia Calculation of fecal iron excretion based on the ratio of total hemoglobin iron to total hemoglobin radioiron gave a daily excretion of 0 33 0 46 mg in the normal subjects Calculations based on the ratio of estimated total body iron to total body radioiron showed a daily excretion of 0 38-0 52 mg One normal subject was given radioactive iron orally to test absorption and had 10% of the isotope incorporated in hemoglobin in 12 days Calculation of fecal iron excretion in the abnormal groups was based on the ratio of total hemoglobin iron to total hemoglobin radioiron Patients with hypochromic anemia had decreased daily fecal excretion of iron (0 032-0 061 mg) One patient with sickle cell anemia had daily excretion of 1 45 mg and one with hereditary spherocytosis 0 3 mg Iron excretion by way of the intestinal tract is probably from bile colon excretions and desquamation of lining cells

Hemolytic crisis was induced with phenylhydrazine in two dogs In one daily fecal excretion of iron during crisis was 0 38 mg and during recovery 0 28 mg In the other before the crisis the excretion was 0 04 mg and during the phenylhydrazine period it was 0 58 mg /day

Iron excretion in sweat was calculated in three normal subjects and one patient with hypoplastic anemia Based on ratio of total body iron to body radioiron normal excretion averaged 0 24-1 56 mg /day In the patient with hypoplastic anemia 24 hour excretion estimate varied from 0 72 to 12 2 mg The small amounts of radioiron in sweat indicates that the skin is not important in iron excretion Excretion of tracer iron in saliva and hair clippings showed measurable but insignificant amounts of iron Estimated combined total daily excretion of iron in urine sweat and feces was 0 5 1 mg /day in normal subjects Although the human body does excrete iron with difficulty the amounts lost are of physiologic and nutritional importance being probably from 0 5 to 1 0 mg /day

[On the whole these observations confirm those of conventional balance studies and indicate that ordinarily because most diets provide for

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(1) J Lab & Clin Med 45 599 615 Ap 1 1955

tramuscularly but many patients given the same prepara tion intravenously in a dose of 4 or 5 ml had moderate re actions (headache backache shivering) an hour or more after the injection High serum iron levels were attained in these trials 10 13 mg /100 ml being reached

The treatment is effective and safe but should be restricted to iron deficiency unresponsive to iron given orally where adequate investigation has disclosed no other cause for anemia The high concentration of iron allows remedy of a given iron deficit by fewer injections than are needed with other preparations Maximal response was achieved in four to nine weeks which is somewhat longer than with other preparations

Correction of Anemia of Malabsorption Syndrome (Non tropical Sprue?) by Oral Administration of Cortisone and Iron Maurice L Kelley Jr Victor W Logan and Lane M Christ[3] (Univ of Rochester) report a case

Woman 48 with diarrhea and weight loss for a year hospitalized because of treatment failure including vitamin B_1 parenterally She was small pale and cachectic with dry skin light brown pig mentation over forearms and abdomen and moderate presacral and pretibial edema The tongue was smooth Blood pressure was 80/60 Physical findings were otherwise within normal limits except for slight hepatomegaly Hematologic examination showed a microcytic hypochromic anemia Liquid brown stools contained numerous fat droplets but were otherwise normal Serum albumin and cholesterol levels blood vitamin A concentration and prothrombin time were decreased Cephalin flocculation was 2+ and the bromsulfalein test showed no retention Glucose tolerance curve was flat Alkaline phosphatase cholesterol ester serum amylase sodium and potassium values were normal as were duodenal trypsin amylase and lipase activity There was free hydrochloric acid in the gastric juice Chest x ray was normal but an upper gastrointestinal series showed coarsening of mucosa of the small intestine with clumping and seg mentation of the barium

She improved slightly on diet and vitamins orally (without folic acid or vitamin B_{12}) and following two 500 cc blood transfusions She was discharged on diet vitamins and 0 2 Gm ferrous sulfate orally three times a day During a relapse three months later 150 mg cortisone daily and ferrous sulfate led to prompt subjective objective and hematologic response After 20 days reticulocytes were 6% after 41 days hemoglobin had risen from 9 2 to 13 6 Gm % Laboratory findings returned to normal although the glucose toler ance curve remained flattened She remained completely well on iron and 37 5 mg cortisone daily

(3) N w E gl d J M d 25 658 661 Ap 21 1955

assimilation of more than 1 mg iron daily an adventitious cause of blood loss is required in order to produce iron deficiency in the adult male. In practice unless manifest blood loss has occurred this indicates need for multiple tests for occult blood in the feces and a complete gastrointestinal x ray examination —Ed]

Intramuscular Iron Therapy in Iron Deficiency Anemia was used in 40 patients by I McLean Baird and D A Podmore[2] (Royal Infirm Sheffield) The preparation was a dextran iron solution with toxicity in mice about one third that of iron saccharate solution stability higher than iron saccharate both in vivo and in vitro and no precipitation in plasma over a wide pH range Its pH is 6 7 it is isotonic with tissue fluids and contains the equivalent of 5% of iron In preliminary control studies on 10 volunteers intramuscular injection caused skin staining when an ordinary intramuscular needle was used but if a needle 2½ in long was inserted in a Z shaped track there was no staining

The 40 patients had hemoglobin deficiency low color index and low mean corpuscular hemoglobin concentration with evidence of iron deficiency in the marrow Patients with hemolysis or continuing blood loss were excluded Total intramuscular dose of iron was 1 000 2 500 mg but a mean calculation showed that 100 mg iron was necessary to raise the hemoglobin 0 34 Gm /100 ml Two patients who did not respond were not truly iron deficient one was found to have uremia and the other bronchogenic carcinoma

No reactions were observed despite serum iron levels as high as 13 8 mg /100 ml Occasional staining of skin occurred due to faulty technic Total dose of iron was given in three or four days to patients in the hospital outpatients received injections twice weekly with satisfactory results Individual hemoglobin response varied considerably in one patient it increased to 101% after seven weeks compared to only 76% in another Average increase of hemoglobin/100 mg iron injected was 0 28-0 48 Gm /100 ml (mean 0 34 Gm) 1 500 mg iron was needed to increase hemoglobin 35% in the average case Hemoglobin response usually appeared after a week of treatment A feeling of well being and improved appetite accompanied the blood response

The preparation was well tolerated in all when given in

(2) Lancet 2 942 946 Nov 6 1954

fants (Fig 69) Four controls required cobalt for anemia and two of the four aged 5 months required iron also

The only symptom in infants with anemia was pallor except in one who had anorexia lassitude and extreme pallor No infant receiving iron cobalt or both from four to eight weeks required additional therapy

The authors conclude that cobalt effectively prevents early anemia of prematurity and that if iron is also given the risk of an iron deficiency anemia developing after the

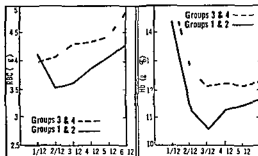


Fig 69 —St t t l ly f a g b m l b l l d d blood ll ou t t m th (C rt y f C l B L d J m U J m l La et 75 79 83 M rch 195)

fourth month is small The mode of action of cobalt may be twofold (1) direct action on erythropoiesis in the marrow and (2) catalytic action enabling available iron to be more readily utilized for hemoglobin synthesis

[The profession has recently learned that its well meaning efforts to supply oxygen efficiently to premature infants may have been the cause of blindness due to retrolental fibroplasia Now one may wonder whether the use of a potentially toxic element such as cobalt in premature infants to prevent their hemoglobin from declining to 10 5 Gm % is a wise procedure Is th s anemia of biologic or only of mathematical significance? What do the prematurely young do to justify the need for the extra hemoglobin? Is the risk of loss of appetite rash nerve deafness or goiter though perhaps small negligible? See the article by Gross *et al* (p 264) —Ed]

Aplastic Anemia (Chronic Erythroblastophthisis) Caused by Autoimmunization R E Bonham Carter I A B Cathie and C Gasser[5] report a case which shows that abnormal plasma substance can inhibit erythrocytic precursors and

(5) S hw m d W h h 84 1114 1116 S pt 25 1954

The findings suggested an iron deficiency state and apparently cortisone increased iron uptake from the gastro intestinal tract Functional insufficiency of the adrenal gland in cases of this kind might also explain some of the cortisone effect Diagnosis of idiopathic steatorrhea seemed justified from the finding of diarrhea malnutrition steatorrhea hypochromic microcytic anemia hypoproteinemia hypocalcemia hypoprothrombinemia low blood vitamin A low glucose tolerance x ray appearance of the small intestine and normal enzymatic activity of the duodenal juice

[Increased iron uptake is inferential —Ed]

OTHER ANEMIAS

Use of Cobalt and Iron in Treatment and Prevention of Anemia of Prematurity in 126 infants is reported by Betty L. Coles and Ursula James[4] (London)

The infants were divided into four groups group 1 controls group 2 received 10 mg cobalt sulfate daily from 1st to 12th day of life group 3 20 mg daily for four to eight weeks *group 4 20 mg cobalt sulfate* and 4 5 Gm ferrous sulfate daily for four to eight weeks The cobalt sulfate being soluble and practically tasteless was readily taken in water or milk No signs of toxicity were noted Blood counts were made at birth one week two weeks one month and monthly to six months All infants were either breast fed or received dried or evaporated milk (20 calories/oz) Vitamins A D and C were given and solids were begun between 3½ and 5 months

The infants in group 2 had a less pronounced fall in hemoglobin levels and red cell counts than those in group 1 but the differences were not significant Those in groups 3 and 4 had significantly higher hemoglobin levels and red cell counts at each examination from two months onward than those in groups 1 and 2 combined Those in group 4 had significantly higher hemoglobin levels from four to six months than those in group 3 From four months on iron deficiency is important in development of anemia in premature in

(4) Journ I La et 75 79 83 Ma h 1955

fants (Fig 69) Four controls required cobalt for anemia and two of the four aged 5 months required iron also

The only symptom in infants with anemia was pallor except in one who had anorexia lassitude and extreme pallor No infant receiving iron cobalt or both from four to eight weeks required additional therapy

The authors conclude that cobalt effectively prevent early anemia of prematurity and that if iron is al o given the risk of an iron deficiency anemia developing after the

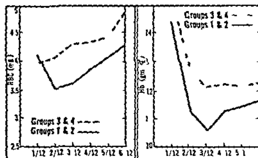


Fig 69 —Stat st l l s of er g b mo lob n le ls d ed blood l ount to x month (Cou t y f C l B L a d Jam s l J [La t 5 983 M r h 1955)

fourth month is small The mode of action of cobalt may be twofold (1) direct action on erythropoiesis in the marrow and (2) catalytic action enabling available iron to b more readily utilized for hemoglobin synthesis

[The profe sion has recently learned that its well meaning efforts to supply oxygen efficiently to premature infants may have been the cau e of blindness due to retrolental fibroplasia. Now one may \ onder whether the use of a potentially toxic el ment such as cobalt in premature infant to prevent their hemoglobin from declining to 10 5 Gm % is a wise proced re Is this "anemia of biologic or only of mathemat cal significance What do the prematurely young do to justify the need for the extra hemoglobin? Is the risk of loss of appetite rash n rve deafness or goit r though perhaps small n gligible? See the article by Gross *et al* (p 264) —Ed.]

Aplastic Anemia (Chronic Erythroblastophthisis) Cau ed by Autoimmunization R E Ponham Carter I A B Cathie and C Gasser[5] report a case which shows that abnormal plasma substance can inhibit erythrocytic precursors and

(5) Schweiz med W h hr 84 1114-1116 Sept. 25 1954

destroy formed elements In principle hemolytic anemias and erythroaplasias are distinct and the following case with coexistent severe hemolysis and erythroblastic aplasia apparently directly related to antibody concentration may be a rare exception

Boy born six weeks prematurely in August 1947 had feeding problems eczema and retarded growth during his first two years At age 2 he had an egg sized swelling in the axilla for several week after vaccination In the next two years upper respiratory symptoms and recurrent generalized lymph node swelling requiring adenotomy appeared Biopsy of an enlarged lymph node at age 4½ showed definite hyperplasia but no reticulosis or leukemia the hemogram was normal At age 5 hemolytic anemia developed after an influenzal infection Lymph nodes and spleen were enlarged and blood studies showed normochromic anemia and reticulocytosis with normal leukocytes and platelet count Serum bilirubin level was slightly and fecal urobilinogen greatly increased Direct and indirect Coombs tests were positive The anemia progressed (Hb 24%) but improved with intensive cortisone treatment transfusions and antibiotics Coombs tests became negative but after withdrawal of cortisone the direct test was again slightly positive

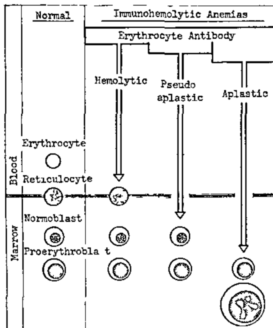
A year after the first hemolytic crisis following another respiratory infection severe anemia developed (Hb 17%) with evidence of intense autoantibody activity Direct and indirect Coombs tests were strongly positive and cold agglutinins of great thermal amplitude were found For the first time there were no reticulocytes in the blood and only 1 5% erythroblasts in the marrow Leukopenia did not appear but platelets were much decreased Splenectomy was performed under protection of cortisone and ACTH Despite a stormy postoperative course the patient improved reticulocytes reappeared and direct and indirect Coombs tests became negative With discontinuance of steroid treatment because of postoperative thrombocytosis hemolytic anemia reappeared again with disappearance of reticulocytes from the blood and almost complete lack of erythroblasts in the marrow Destruction of erythrocytes was extremely rapid and the anemic crisis could be controlled only by repeated blood transfusions

In January 1954 after massive doses (250 mg daily) of cortisone for 19 days the marrow was completely changed for the first time in six months there were 68% erythroblasts and 75% reticulocytes in the blood Hemoglobin rose to 56% and later even higher Coombs tests were negative When because of side effects cortisone was reduced to 55 mg /day the erythroblasts and reticulocytes decreased and Coombs tests were slightly positive By increasing cortisone dosage the child remained in good condition and the hemoglobin level was maintained without transfusions

This case demonstrates a relationship between destruction of erythrocyte precursors and serologically demon

strated erythrocyte antibodies with an extreme effect i e the antibodies affected not only erythrocytes and reticulocytes but also nuclear precursors in the marrow which led *to prolonged and practically complete erythropoietic aplasia* (Fig 70)

Acquired hemolytic anemia can become aplastic or pseudo aplastic i e there can be either destruction of or a dis



Fg 70—(Co rte f B h m C t R E t l S hw z. m d W h b 84 1114 1116 S pt 25 1954)

turbance in maturation of erythrocytic elements caused by abnormal autoimmune substances For this reason in aplastic anemias previous or still existing hemolytic processes should be looked for and appropriately treated (cortisone or ACTH splenectomy) A normal or reduced reticulocyte count is unusual in hemolytic anemia but cannot be excluded *its appearance may be a sign of severe impairment*

of erythropoiesis So called exhaustion of marrow is not the correct explanation in certain cases of aplastic anemia

[A similar concept has been suggested as an explanation of chronic congenital aregenerative anemia (pure red cell anemia) associated with isoimmunization by blood group factor A in an article by C H Smith (Blood 4 697 705 June 1949) Leukocyte and platelet agglutinins may also alter the appearance of the parent cells in the marrow—Ed.]

Splenectomy for Pure Red Cell Hypoplastic (Aregenerative) Anemia Associated with Autoimmune Hemolytic Disease Report of a Case apparently unique is presented by Gustave Eisemann and William Dameshek[6] (Boston)

Woman 58 hospitalized with thrombophlebitis Red cell count was 3 200 000 hemoglobin 8 25 Gm and white cell count 2 350 Dicumarol® was administered and continued on ambulatory basis A month later both liver and spleen were enlarged red cell count was 2 600 000 and hemoglobin 7 Gm later dropping to 1 800 000 and 5 3 Gm White cell count was 3 800 with 78% neutrophils 15% lymphocyte 4% monocytes and 3% eosinophils platelets were 475 000/cu mm (Dameshek method) Prothrombin time was 16 seconds (control 14 seconds) Fecal urobilinogen was 130 mg a day The hemolytic index was 42 (normal about 20) Red cell hypotonic fragility was normal The direct Coombs test was strongly positive Bone marrow was hypocellular myeloid erythroid ratio was 12 1 nucleated red cells were conspicuously reduced and there was apparent maturation arrest of erythroid cells at the normoblast A level

Due to lack of erythrocyte production and excessive blood destruction she eventually required weekly blood transfusions and had received 20 when seen by the authors nine months after onset Red blood cells numbered 1 900 000 with hemoglobin 6 2 Gm hematocrit 24 reticulocytes 0 3% and platelets 300 000 After two months of complete absence of reticulocytes in the blood and of nucleated red cells in the marrow splenectomy was performed Spleen weighed 600 Gm and showed generalized hyperplasia of normal tissue and moderate hemosiderosis There was no appreciable erythrophagocytosis or myeloid metaplasia The 18th day the first reticulocytes appeared in the blood and large numbers of erythroblasts in bone marrow She maintained normal blood levels without transfusions

This is the first known report of autoimmune hemolytic disease with prolonged aregenerative anemia and the first in which hypersplenism was responsible for lack of erythropoiesis and pure red cell anemia Recovery of complete bone marrow erythropoiesis following splenectomy strongly suggests a splenic factor that acted on red cell precursors inhibiting their maturation Delay for more than two weeks of erythropoiesis after splenectomy further suggested a humoral factor in the spleen requiring at least two weeks for removal from the circulation

(6) N w Engla d J Med 251 1044-1048 Dec 23 1954

The fundamental mechanism of autoimmune hemolytic anemia is unknown Thrombophlebitis in the present case may have set off a trigger mechanism causing autosensitization Splenic enlargement may have resulted in hypersplenic action with a particular effect on bone marrow nucleated red cells or possibly the specific aregenerative state of nucleated red cells in the marrow resulted from direct action of incomplete erythrocyte antibodies on red cell precursors with complete inhibition of erythropoiesis Splenectomy may have removed a large source of antibody producing tissue as shown by diminution in strength of the Coombs test

The occasional striking benefit of splenectomy in hypoplastic anemia or bone marrow failure suggests that splenectomy be strongly considered in all aregenerative anemias

[This experience is hard to explain otherwise than as an effect of the spleen upon erythropoiesis In practice it cannot be counted on to occur—Ed.]

Pure Red Cell Anemia in Patients with Thymic Tumors Selective bone marrow aplasia involving erythropoiesis but not leukocyte and platelet production is rare and thymic tumor has been observed in some of the few adults fully investigated J N Marshall Chalmers and K Boheimer[7] (St George s Hosp and Med School London) report on two patients One also had myasthenia gravis both had thymomas but recovered after thymectomy splenectomy and ACTH therapy

The authors suggest two hypotheses to explain these unusual cases (1) Endocrine dysfunction may be responsible since the thymus is enlarged in some cases of thyrotoxicosis and Addison s disease The polycythemia sometimes seen in Cushing s syndrome might be regarded as the opposite extreme of aplasia especially since these two patients responded to ACTH (2) Lymphoid proliferation in the thymus marrow and possibly other sites may in some way impede erythropoiesis Depending on the degree of such interference removal of the tumor may either correct the anemia or have no effect In the first patient temporary hematologic remission occurred after total removal of the thymoma but in the second insignificant changes followed operation possibly because some thymus tissue remained

(7) B M J 2 1514 1518 Dec. 25 1954

Splenectomy also seemed to cause temporary improvement in the first but had no effect on the second patient While ACTH given earlier caused no significant hematologic changes both had prompt and well maintained responses to ACTH given after splenectomy This has also been observed by other investigators in patients with erythroid hypoplasia but no recorded evidence of thymoma

Spontaneous recovery from pure red cell anemia has been reported but in the present instances it appears that the responses were related to surgery or ACTH therapy In the second patient hematologic relapse following discontinuation of ACTH after splenectomy and subsequent remission when the hormone was reinstated reinforces this view Apart from blood transfusion no other treatment including riboflavin was of avail in this patient

Simultaneous Occurrence of Benign Thymoma and Refractory Anemia was observed in two patients by Joseph F Ross Stuart C Finch Russell B Street Jr, and John W Strieder[8] (Boston Univ)

CASE 1—Woman 44 had an asymptomatic substernal tumor Severe anemia developed and marrow showed marked decrease in erythropoietic elements Acquired hemolytic anemia with positive Coombs reaction was relieved by splenectomy but only congestive changes in the spleen were revealed Severe anemia and hypoplastic erythropoietic marrow persisted Removal of the mediastinal tumor proved to be a thymoma did not affect the anemia which was not relieved by hemopoietic agents ACTH or cortisone Anemia was controlled by 174 transfusions but signs of hemochromatosis and severe diabetes mellitus developed

CASE 2—Woman 45 had severe anemia with decreased marrow erythropoietic activity Pleural effusion appeared and a mediastinal tumor was resected, which proved to be a benign thymoma Severe anemia of nonhemolytic type with negative Coombs reaction persisted despite administration of hemopoietic agents and cortisone Transfusions to date numbering 83 were necessary to maintain blood hemoglobin at life sustaining levels Skin pigmentation due to deposition of hemosiderin appeared

Three instances of benign tumors associated with acquired hemolytic anemia have been recorded Two were ovarian dermoid cysts splenectomy was not beneficial but prompt recovery from anemia followed removal of the cysts [It is of interest that Gorer has shown that such cyst fluid readily agglutinates sensitized red cells —Ed]

(8) Blood 9 935 95 October 1954

Relation of benign thymoma to refractory anemia presents the possibilities of (1) simultaneous occurrence by chance alone (2) thymomas causing the anemia (3) anemia causing the thymomas or (4) some common etiologic factor

Seven patients whose cases are recorded had benign tumors of thymic origin All had decreased erythropoietic activity and anemia refractory to all therapy except transfusion In four leukocytes and platelets of blood and granulopoietic and megakaryocytic elements of marrow were normal In two leukocytes platelets and granulopoietic and megakaryocytic elements were reduced These two patients died as did one with normal leukocytes and platelets

Among cases in the literature was that of a man 56 with myasthenia gravis who had severe pancytopenia and died following agranulocytosis thymoma found at autopsy was histologically benign Refractory anemia was reported in a woman 58 with lymphoepithelioma of the thymus marrow showed decrease in red cell precursors with normal myeloid and megakaryocytic elements Another woman 58 had refractory anemia associated with a benign epithelial tumor of the anterior mediastinum marrow showed mild hypoplasia of erythroid elements Blood was rapidly restored to normal after removal of the tumor Pancytopenia in a youth 20 with a cystic fibrous tumor of the thymus and extreme hypoplasia of bone marrow has been described In a man 48 with myasthenia gravis who had profound anemia marrow biopsy disclosed absence of all red cell precursors although leukocytic and megakaryocytic elements were normal X rays of the chest did not reveal a tumor but operation disclosed a large thymoma its removal was followed by return to normal of red cell precursors but there was relapse Splenectomy and large doses of ACTH resulted in favorable response of marrow and peripheral blood Another course of ACTH was given after relapse and anemia and myasthenia gravis were controlled for a year A woman 62 with severe refractory anemia responded to ACTH therapy then relapsed Slight transient hematologic improvement followed removal of a thymoma Leukocytes platelets and granulopoietic and megakaryocytic elements

were normal in a man 47 with profound normocytic anemia and complete aplasia of erythropoietic elements Red cell elements appeared in the marrow and peripheral blood returned to normal after removal of a thymoma

There is good evidence that there is a casual connection between thymoma and refractory anemia Study of the thymus and marrow is recommended whenever either condition is observed There may be significant deviation from the normal histologic pattern in a normal sized thymus or thymoma may be present which cannot be visualized radiologically Surgical exploration and thymic resection should be considered in patients with refractory anemia

Blood Changes Associated with Disseminated Tuberculosis Report of Four Fatal Cases and Review are presented by James R Fountain[9] (Leeds) Although anemia is common to all forms of tuberculosis it is rarely severe and usually normochromic or hypochromic In a study of 63 cases of generalized miliary tuberculosis Chapman and Whorton noted moderate normochromic anemia in 84% Lowest hemoglobin level was 43% but most ranged from 65 to 85% In 11 of 49 patients a relative neutrophilia was associated with leukopenia The hematologic picture in two cases resembled aplastic anemia and in another leukoerythroblastic anemia Others have described aplastic anemia in miliary tuberculosis and bone marrow infiltration seems not to be uncommon Chapman and Whorton found it in 33 of 37 cases of miliary tuberculosis at necropsy Tuberculous splenomegaly and leukemoid reactions have also been reported in tuberculous patients

The four cases presented displayed hematologic abnormalities with pancytopenia in all from the outset Anemia was severe in three the hemoglobin level was below 50% the lowest being 32% Macrocytosis was present in all and bone marrow in three showed marked depression of hemopoiesis In Cases 1 and 2 the bone marrow picture suggested aplastic anemia although aleukemic lymphatic leukemia was difficult to eliminate Persistent reticulocytosis and leukoerythroblastic anemia in the absence of myeloid metaplasia indicated that some marrow function remained The leukoerythroblastic anemia might possibly be explained by

(9) Brit M J 2 76-79 July 10 1954

infiltration of bone marrow by the tuberculous process In Case 3 bone marrow was normal and absence of splenomegaly contraindicated a hypersplenic mechanism as the cause of cytopenia Case 4 had many hematologic features similar to those in the other cases but postmortem examination showed widespread visceral infiltration with lymphoid cells indicative of coexisting lymphatic leukemia Although lymphatic leukemoid reactions with miliary tuberculosis have been reported presence of leukemia and generalized tuberculosis must be extremely rare The patient previously had been in good health with no suggestion of tuberculosis Possibly a latent focus of tuberculosis was activated by the developing leukemia with resultant widespread dissemination

Clinically these cases were primarily problems in diagnosis The cardinal feature was the marked hematologic changes with pyrexia and progressive weight loss In only one was a definite diagnosis reached before death following biopsy of an enlarged cervical lymph node In Case 1 there was no evidence of tuberculosis and routine investigations for tuberculosis in Case 3 did not reveal the disease although latterly chest x rays were suggestive A clinical diagnosis of aleukemic lymphatic leukemia was made in Case 4 and only at necropsy were the enlarged lymph nodes and spleen found to be the seat of extensive tuberculous disease

With chemotherapy available for tuberculosis an early diagnosis must be made Pancytopenia with or without *depression of blood forming elements in bone marrow* pyrexia and loss of weight should suggest tuberculosis in the absence of other causative factors Presence of lymphadenopathy demands a biopsy to differentiate from Hodgkin s disease or lymphosarcoma and aleukemic lymphatic leukemia Bone marrow should be examined for miliary tubercles Culture of blood obtained by bone marrow aspiration together with guinea pig inoculation should also be carried out

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(9) Brit M J 2 76 79 July 10 1954

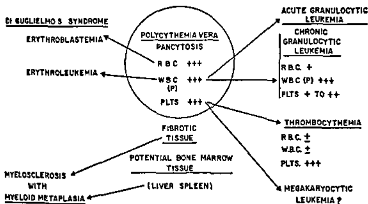


Fig 71—Pol ythem d l ted —th my lopr L ti e d m (C rt y o D m h k W B ll N w E gl d M C t r 16 53 63 J 19 4)

orders (Fig 71) Marrow proliferation may be dominant at one time in one direction and later in another thus producing apparently different syndromes This unified concept of an apparently diverse group of diseases although by no means proved has been of great value in understanding these disorders which otherwise present many common features and have a common site of proliferative activity

[One good diagram such as this author's saves many words—Ed.]

Treatment of Polycythemia Vera with Daraprim® [2 4-diamino 5 (p chlorphenyl) 6 ethyl pyrimidine] or pyrimethamine an antimalarial drug antagonistic to folic and folinic acids *is described with six case reports by Raphael* Isaacs[2] (Chicago) Three reactions noted were (1) an orderly reduction in number of red blood cells (2) no marked changes in number of leukocytes or platelets and (3) amelioration of symptoms associated with polycythemia vera Six patients were given 25 mg daraprim® once daily after breakfast until the red blood cell count approached 4 500 000 5 000 000/cu mm At this point dosage was continued indefinitely unless red blood cell count continued to fall The dose was then reduced to 12 5 mg daily or if the fall was rapid discontinued until recovery was evident There were no special dietary restrictions Theoretically a diet

(2) J A M A 156 1491 1493 Dec 18 1954

POLYCYTHEMIA

Some Observations in Polycythemia Vera A few features of this disease, including itching after a bath myelosclerosis and myeloid metaplasia of the spleen and the central position of polycythemia vera in the myeloproliferative syndromes have been insufficiently stressed according to William Dameshek[1] (Tufts College)

Intense itching after a bath occurs in about one third of patients with polycythemia vera Some relief follows an induced remission but the symptom may persist slightly even when the polycythemic state is ' burnt out This itching seems more or less specific for polycythemia vera and differs from the generalized and constant itching of Hodgkin s disease and lymphosarcoma

After a variable period of intense bone marrow activity during which it is difficult to prevent blood counts from building up to high levels the polycythemic state often seems to become static for a year or five years or longer Anemia develops imperceptibly and gradually becomes more severe This burnt out polycythemia is associated with gradually increasing fibrosis of the marrow White cells and particularly megakaryocytes and platelets may remain at high levels or even increase Early white cells and occasional nucleated red cells are seen Simultaneously splenomegaly becomes more pronounced It has become increasingly apparent that agnogenic myeloid metaplasia and the postpolycythemic state of myeloid metaplasia are identical As the condition progresses white cells and finally platelets are diminished The spleen and liver increase even more in size, and the abdomen becomes more protuberant and uncomfortable sometimes with considerable pain In this situation little can be done and treatment is merely symptomatic

Polycythemia vera chronic granulocytic leukemia myeloid metaplasia with myelosclerosis the Di Guglielmo syndrome and thrombocythemia although superficially distinct entities may actually be variants of a more generalized disturbance and may be considered as myeloproliferative dis

(1) Bull. New E gla d M Cent r 16 53 63 Jun 1954

Further Observations on Immune Leukopenias and Agranulocytoses caused by leukocyte agglutinins are reported by S Moeschlin[3] (Univ of Zurich) Of 14 cases studied 5 were due to pyramidon® 1 to sulfapyridine 3 to lupus erythematosus and 1 each to virus pneumonia mononucleosis Felty s syndrome plasmacytoma and tuberculosis of the spleen (?) Similar cases have been reported by several other authors and immune agranulocytoses have been produced experimentally in rats and rabbits with agglutinating antileukocytic serums

Man 57 after receiving sulfapyridine (4 Gm daily) for three weeks for Duhring's disease had neutrophilic agranulocytosis (leukocyte count 1 300) with persistence of characteristic eosinophilia during agranulocytosis of about 50% Penicillin and strepto

LEUKOCYTE AGGLUTINATION WITH SULFAPYRIDINE AGRANULOCYTOSIS

	DAY 2	3	5	9	11	15	30
Agranulocytos ser m	+++	++	+−	−	−	−	−
Heated 30 m n t 5 C	++++	+++	+	+−	−	−	−
Heated 30 m n 65 C	−	−	−	−	−	−	
W th lf py din (20 mg /100 ml)			++++	+++	++	+−	
Pl w h d leukoc t s f lf pyrid t eat d control			+−	+−	−	−	
Cont ol serum	−	−	−	−	−	−	
W th s lfapy d n (20 mg /100 ml)			−	−	−	−	

mycin produced rapid recovery Within a week the leukocyte count increased to 1 000 and in 14 days reached 22 000 with 17 500 neutrophils The eosinophil level dropped during the first phase of recovery and attained a maximal value of 5 000 during leukocytosis The agranulocytic serum showed strongly po itive agglutination with leukocytes of similar blood group (table) During the recovery phase the serum showed no agglutination but the addition of 20 mg/100 ml sulfapyridine produced definite agglutination This did not occur when sulfapyridine was added to control serum

These observations indicate that the mechanism of sulfapyridine agranulocytosis was similar to that previously described for pyramidon® agranulocytosis The first change is not damage to marrow but enormous destruction of leukocytes in the lung capillaries and perhaps also in the spleen and liver because of massive agglutination of leukocytes in peripheral blood This results in an excessive demand on

(3) S hw z. m d. W b schr 84 1100 1103 S pt. 25 1954

rich in folic acid would inhibit effectiveness to some degree but actually this was not the case

As red cell count decreased number of large red cells in creased and range in sizes increased from microcytes (3 7 μ) to macrocytes (12 3 μ) The blood picture resembled that in pernicious anemia but the large red cells were both round and oval and not predominantly oval or oblong Im mature red cells with normoblastic nuclei present at times in peripheral blood of patients with polycythemia were of the large type Multilobed polymorphonuclear neutrophils appeared

Dosage varied with each patient The blood was checked weekly until the response was determined and monthly thereafter There was about a two week latent period of re covery when therapy was stopped No toxic symptoms were noted in a year One patient attributed diarrhea to the drug but diarrhea reappeared when the patient had not had dara prim* for four weeks One patient noted soreness of the tongue when the red blood cell count was 4 400 000 leuko cyte count 11 600 and hemoglobin level 13 4 Gm /100 cc Lesions cleared with silver nitrate without discontinuing the drug

Signs of improvement included decrease in pruritus ces sation of headaches and joint pains decrease in blood pres sure and a feeling of well being In the doses used and with the control based on red blood cell count no symp toms of antifolic acid poisoning were noted At the height of the effect when the blood cell count is low there is marked change in appearance of the marrow with megalo- blastic forms and a decrease in the normoblastic picture characteristic of polycythemia vera Because of the sensi tivity of rapidly differentiating tissue to antifolic acid drugs presumably pregnancy would be a contraindication to use of the drug

[Analysis of the hematologic data suggests that the cessation of venesection (previously employed to control the condition in each pa tient) with resulting conversion from hypochromic to normochromic red cells had much to do with the reported falls in red counts In only one of the five patients on whom such data were given did the hemoglobin decline in four it actually rose during therapy! The lack of effect on white cell levels also suggests that in the dosage used the drug dis played little antifolic action on red cell precursors More clinical trials are needed.—Ed.]

scopically clumps seemed larger and firmer Serum maintained its capacity to agglutinate leukocytes after splenectomy and during cortisone treatment although leukocyte values were almost normal and there was only moderate relative granulocytopenia Anemia however remained a therapeutic problem

It seemed doubtful that the substance in this patient s blood was an agglutinin in the immunologic sense since it was thermolabile and serum gamma globulin was not increased It was assumed though unproved that the substance which coated erythrocytes and agglutinated leukocytes was the same Enlargement of the spleen increased reticulum cells and high titer of splenic blood implicated the reticuloendothelium as the site of origin but splenectomy had no effect Smears of the spleen showed no abnormal increase in phagocytic activity of splenic cells or of leukocytes

Leukoagglutinins V Leukoagglutinins in Chronic Idiopathic or Symptomatic Pancytopenia and in Paroxysmal Nocturnal Hemoglobinuria Studies on antibodies in serums of patients with acquired hemolytic anemias and thrombocytopenic purpuras have stimulated comparable studies on leukocytes Leukolysins and in one instance a powerful leukocidin have been demonstrated in certain granulocytopenias Serum of a patient with granulocytopenia due to pyramidon® wa capable after ingestion of the drug of agglutinating normal human leukocytes in vitro and injection of the whole blood into a normal person caused a rapid fall in white count Leukoagglutinin has also been found independent of sensitization or intoxication

J Dausset A Nenna and H Brecy (Paris) using a special test studied over 2 000 normal subjects 500 patients with various diseases and 102 with leukopenia Serums were negative for leukoagglutination (Fig 72) except for 19 in which it was consistently present (Fig 73) in at least 50 repeated determinations Patients whose serums showed leukoagglutinin were (1) one with agranulocytosis with pyramidon® hypersensitivity (2) one who had received 305 transfusions (3) three with paroxysmal nocturnal hemoglobinuria (Marchiafava Micheli syndrome) (4) five with malignant hemopathies and (5) nine with aplastic or hypo

(5) Blood 9 696 720 J ly 1954

the bone marrow with an increase of immature cells and finally in severe cases in complete exhaustion of marrow cells The agranulocytic process is to be interpreted as resulting from an antigen antibody reaction whereby leukocytes become involved secondarily (agglutination) It seems most likely that antibodies (as with erythrocytes in certain hemolytic anemias) on the surface of the leukocytes react with the antigen to produce the agglutination

[However such reactions may involve marrow granulocyte precursors as well—Ed.]

Leukocyte Agglutinins in Case of Chronic Granulocytopenia and Hemolytic Anemia Curt Wasastjerna[4] reports the single instance of such agglutinins revealed in a systematic study of all cases of granulocytopenia observed at Maria Hospital Helsingfors during one year He recognizes that hemolytic anemia thrombocytopenia and leukopenia may each be caused by antibody like substances in the blood

Woman 39 had anemia low leukocyte counts and relative granulocytopenia for seven years Then anemia increased and she received several blood transfusions An acute infection six months later caused impairment and rapid decrease in erythrocyte count. There were a slightly increased reticulocyte count increased osmotic red cell fragility and spherocytes in the smears Marrow findings were essentially normal She was never jaundiced Splenectomy after the second relapse gave no significant benefit Cortisone gave some relief but not complete remission The course was mostly afebrile although there were some acute infections Except during these episodes sedimentation rate was normal Except for a little protein during one infection urine was normal

The Coombs reaction was weakly positive with two antihuman globulin serums and negative with a third No agglutination was observed when serum was tested with six types of O cells at room temperature and at 37 C The indirect Coombs reaction was negative as were tests for L F cells Results of agglutination tests with patient s serum and a leukocyte suspension from another person of group O were positive on seven occasions all controls had negative results Titers at room temperature and 37 C were the same but agglutination was much weaker at 4 C Heating to 56 C for 30 minutes completely inactivated serum agglutinating capacity Agglutination by serum separated from splenic blood seemed more active than that from peripheral blood The spleen serum agglutinated only in one additional tube but both macroscopically and micro

(4) Acta med sca d 149 3 360 19 4

plastic anemia Excluding the patient with multiple transfusions leukopenia with neutropenia was the only common clinical feature and it seems reasonable that the leukoagglutinin may have been largely responsible In the patient with pyramidon* sensitization the leukoagglutinin was present only with granulocytopenia In all others leukoagglutinin titer followed (though imperfectly) fluctuations in white cell count and agglutinating substance was present only in serums of patients who were or had been leukopenic Apparently the test findings may remain positive after leukopenia has passed as is true for panantibodies in hemolytic anemias In two patients following transfusions with blood containing leukoagglutinin there was marked leukopenia

Simultaneous leukopenia anemia and thrombocytopenia in most of these patients is difficult to explain In most antiplatelet or anti red cell antibodies could not be demonstrated Four however showed panantibody active only against trypsinized red cells and in one thromboagglutinin was demonstrated before splenectomy To explain disturbance of all three cell types in both marrow and peripheral blood it must be supposed that technics for detection of specific agglutinating antibodies were not sufficiently sensitive that the antileukocytic substance had a polyvalent action on a protein substrate common to all three series or that thrombopenia and anemia are produced by some unknown mechanism

By analogy with immunologic hemolytic anemias antileukocytic substances fulfil present criteria for antibodies and may play a causative role in various leukopenias The leukoagglutination test may permit differentiation of toxic from immunologic leukopenias

↓ Leukopenia thrombocytopenia and rarely hemolytic anemia are associated with the L.E cell phenomenon which is discussed in the next article —Ed

Differences in Susceptibility of Polymorphonuclear Leukocytes from Several Species to Alteration by Systemic Lupus Erythematosus Serum Application to a More Sensitive L E Phenomenon Test Specificity and diagnostic value of the L E cell phenomenon have been amply verified and the L E test has shown that systemic lupus erythema

F g 72 —Neg t v eact on to leukoagglut ation test. (C rte y f Da s t J t l Blood 9 696 720 July 1954)



F g 73 —H ghl po t r a t n (+++) to leukoaggl t t on t t (C rt y of D s t J t l Blood 9 696-720 July 1954)

in chickens and mice it is caused by a filtrable submicroscopic agent presumably a virus transmitted from one generation to another directly through the embryos Chickens carrying the virus of lymphomatosis and transmitting it through eggs to their offspring show no symptoms of the disease when they lay the eggs However the hatched eggs contain the virus since extracts prepared from such embryos reproduce leukemia when inoculated into susceptible hosts Young chicks hatched from infected eggs appear healthy but transmit the virus to their offspring Only when carrier hosts reach middle age does leukemia usually develop but such chickens also may never have lymphomatosis They may die before the agent is activated or the agent may fail to become activated Lymphomatosis would then skip a generation or two Susceptibility of a chicken to experimental infection with the agent of lymphomatosis appears limited to the first few days after birth

In certain families of mice leukemia develops more frequently than in the average population and by selective breeding families of pedigreed mice can eventually be established in which incidence of spontaneous leukemia is extremely high In one such family (Ak) the albino mice are in perfect health when young over 80% of males and females develop leukemia however at middle age (i e usually before age 1 year) In most animals the peripheral blood shows characteristic changes but the peripheral blood picture may not be typical unless the animal is examined shortly before death Bone marrow study is more dependable diagnostically The author recently demonstrated that leukemia in Ak mice is actually caused by a filtrable agent transmitted from one generation to another directly through the embryo Previous attempts to demonstrate such an agent failed until newborn suckling mice (under 16 or better under 12 hours old) were used for inoculation of the leukemic extracts

Extracts prepared from Ak and also C58 leukemic mice may induce salivary gland carcinomas yet these strains serving as donors of tissues do not exhibit spontaneous salivary gland carcinomas It is possible that both inbred lines may carry two different oncogenic agents one for leukemia and the other capable of causing salivary gland

tosus is a protean and fairly common disease surpassing Addison s anemia and Hodgkin s disease in frequency Because certain factors in the reaction—desoxyribonucleic acid (DNA) desoxyribonuclease (DN ase) and a specific inhibitor of DN ase—are intracellular Ana E Carrera May Virginia Reid and N B Kurnick[6] (Tulane Univ) considered that a more sensitive L E test of practical application could be developed if cells of some readily available animal species were found to be more sensitive than human leukocytes That leukocytes from bone marrow of heterologous species are susceptible to the L E phenomenon has been reported previously

Leukocytes from peripheral blood of 12 species were tested by counting the number of L E cells globs (free homogeneous basophilic masses) droplets and rosettes per 1 000 white cells and per 1 000 polymorphonuclear cells after two hours incubation in L E serum Controls consisted of similar preparations using normal human serum and homologous plasma

Species showed a wide range of susceptibility to the L E phenomenon When results were quantitated according to L E manifestations per 1 000 polymorphonuclears the scale of susceptibility was chicken horse mouse guinea pig rat dog monkey rabbit cat man, raccoon and hamster Sensitivity of the chicken and horse is almost 100 times that of man Classic L E cells were produced from leukocytes of most species tested The authors believe a highly sensitive L E test can be performed using chicken horse guinea pig or dog instead of human leukocytes

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LEUKEMIA AND RELATED DISORDERS

Is Leukemia Caused by a Transmissible Virus? A Working Hypothesis is presented by Ludwik Gross[7] (V A Hosp Bronx, N Y) Leukemia appears more frequently among members of certain families than in the average population not only in chickens mice and cattle but also in human beings Direct experimental evidence suggests that at least

(6) Blood 9 1165 1171 Decembe 1954
(7) Ibid pp 557 573 J e 19 4

Early Atypical Manifestations of Leukemia Diagnosis of leukemia usually is not difficult but initial manifestations may be atypical and precede onset of clinically recognizable disease by several years Hematologic changes are not specific and consist of combinations of anemia leukopenia and thrombocytopenia with hyperactive marrow the spleen is usually not palpable or only slightly enlarged These cases often resemble the syndrome designated as primary splenic panhematopenia

Gordon C Meacham and Austin S Weisberger[8] (Western Reserve Univ) discuss 10 patients observed in five years Six later developed typical rapidly fatal leukemia One each died of reticulum cell sarcoma aplastic anemia and hemorrhage associated with thrombocytopenia The one survivor was slowly developing hematologic changes strongly suggestive of leukemia Average time from first abnormal hematologic findings to onset of clinically recognizable leukemia in six was 20 6 months In none of these could the diagnosis of leukemia be established initially

When first seen all had anemia hemolysis was present in seven leukopenia in eight and neutropenia in eight All but one had thrombocytopenia Marrow aspirations revealed normal or increased cellular activity of the erythroid granulocytic and megakaryocytic elements The spleen was palpable in only one Splenectomy in eight gave only transitory benefit The spleen revealed no specific morphologic lesion Hence absence of immature cells in the peripheral blood and marrow and absence of leukemic infiltration in the spleen does not rule out the possibility that leukemia will develop

These cases are indistinguishable from those described as splenic panhematopenia Follow up studies of cases previously described as primary splenic panhematopenia may reveal ultimate development of leukemia lymphoma or other diseases in a significant percentage

[This has been precisely our experience in a few such patients followed for several years Consequently the diagnosis of primary splenic neutropenia, if it exists as an entity can safely be made only retrospectively some months or years after splenectomy —Ed.]

Giant Follicle Hyperplasia Study of Its Incidence Histopathologic Variability and Frequency of Sarcoma and

(8) A I t M d 41 780 797 O t ber 1954

carcinoma when inoculated into newborn C3H mice Conversely Ak and C58 mice may carry a single agent potentially capable of causing either leukemia or salivary gland carcinoma

Although no experimental evidence is available on the nature of leukemia in cattle and human beings the possibility of a transmissible agent should be considered Leukemia has been observed in members of the same family in cattle in two or three successive generations Concerning human beings there is one published report of 3 and possibly 4 of 7 siblings who died of acute leukemia, and 8 of 22 individuals comprising this family s second and third generation had cancer Numerous records show leukemia in three successive generations

Familial occurrence of leukemia and other malignant tumors could be explained by the following working hypothesis there may exist a group of submicroscopic cell free oncogenic agents individually distinct (some causing leukemia others causing different malignant tumors) transmitted directly through the germinal cells from one generation to another These agents would usually exist in an inactive form and would cause no apparent harm to their carrier hosts Occasionally however prompted by obscure but presumably varied trigger stimuli they might change into formidable pathogens Activated oncogenic agents would cause rapid multiplication of cells harboring them resulting in development of leukemia or other malignant new growth Since however activation would usually occur in middle aged hosts survival of the agent would have been already assured since transmission to offspring would have occurred before activation Leukemia and other malignant tumors would therefore be essentially egg borne virus diseases Development of leukemia or other malignant tumor could be regarded as the result of activation frequently merely accidental of an oncogenic agent hitherto masked and carried by the host since birth Since in many perhaps most instances the agents would never become activated (though they would continue being transmitted from one generation to another) only now and then would leukemia or other malignant new growth develop in some members of certain families

In one patient with panhematocytopenia who had suc cessful splenectomy lymphosarcoma with rapid general dis semination developed seven years later and he died An other had suggestive evidence of reticulum cell sarcoma metamorphosis nine years after splenectomy Following original biopsy diagnosis of giant follicle lymphoma sar coma occurred in four

The relative ease with which x ray or radioactive phos phorus therapy controls benign follicular hyperplasia in lymph nodes and spleen justifies an optimistic prognosis in this disease when sarcomatous changes develop treat ment and prognosis must be readjusted The etiology of giant lymph follicle hyperplasia is entirely unknown The relatively benign character suggests a reversible or control lable physiologic functional response rather than progres sive irreversible pathologic malignant mutation of cells in the enlarged germinal centers

Autoimmune Hemolytic Anemia of Malignant Lympho cytic Disease Martin C Rosenthal Anthony V Pisciotta Zacharias D Komninos Henry Goldenberg and William Dameshek[1] (Boston) studied 24 patients with malignant lymphocytic disease in whom the typical features of hemo lytic anemia developed during their illness There were 20 with chronic lymphocytic leukemia 3 with lymphosarcoma and 1 with giant follicular lymphoblastoma The leukemia group mostly men (15) were aged 47 78 the other four pa tients were aged 35 58 The anemia in these patients is referred to as overt since the typical features of hemolytic anemia are present in contrast to a small percentage whose *anemia is not typical and is classed as occult*

Uncomplicated chronic lymphocytic leukemia was diag nosed in 11 of the 20 cases before onset of anemia An average of 33 months elapsed before symptoms of hemo lytic anemia appeared Spray irradiation was given to five of these just before development of anemia and local irradia tion had been given to two The other patients were sus pected of having leukemia for some time before onset of anemia In one patient in the sarcoma group hemolytic ane mia developed six months after diagnosis of lymphosar coma The other three patients had anemia before diagnosis

(1) Blood 10 197 226 M h 1955

Secondary Hypersplenic Complications is reported by Theodore S Evans (Yale Univ) and Charles A Doan[9] (Ohio State Univ) It is particularly important to differentiate monocytopenia and pancytopenia as due either to central marrow invasion or damage or to some peripheral mechanism—with special reference to one of the so called secondary hypersplenic or dysplenic syndromes

In chronic splenolymphatic disease (giant follicle hyperplasia or follicular lymphoblastoma) a relatively benign reticulum cell hyperplasia appears to be partly responsible for development of abnormally enlarged germinal follicular centers Unlike other lymphomas this gross pathologic picture has been described as a localized or generalized phenomenon occurring in both sexes with similar relatively benign cytologic and clinical characteristics from birth through the sixth decade Since 1942 of about 300 patients followed at the Lymphoma Clinic in Columbus 13 (4 3%) have had giant follicle hyperplasia representing 0 8% of all lymphatic dyscrasis observed To these are added 3 patients from the New Haven Clinics making 16 patients followed for months or years

Two significant characteristics of giant follicle lymphoma are early splenic involvement (more common than bone marrow invasion) and a relatively chronic clinical course The combination makes patients peculiarly susceptible to secondary hypersplenic cytopenic episodes Of the 16 patients 11 had splenomegaly 8 required splenectomy for acute cytopenic episodes When the spleen becomes involved and enlarged hypersequestration of one or more circulating blood cell types is facilitated by its reservoir system Three had acute hemolytic anemia two had thrombocytopenic purpura one profound neutropenic leukopenia and thrombocytopenia and two peripheral pancytopenia involving all formed elements of the blood Each syndrome was promptly reversed by removal of abnormal splenic tissue If the original cytopenic syndrome recurs an accessory spleen should be suspected its removal is followed by a second remission Only rarely do the R E cells participate in hyperphagocytosis in tissues other than the spleen specific suppressive therapy is required if this does occur

(9) Ann Int Med 40 851 880 May 1954

ACTH or compounds E or F may do so Splenectomy is not to be considered lightly since most patients are already quite ill Only when therapy with ACTH or related hormones is unsuccessful should the ancillary procedure of splenectomy followed by hormonal therapy be pursued Several patients were readily controlled by hormonal therapy alone

Histiocytic and Monocytic Leukemia Clinical Hematologic and Pathologic Differentiation is presented by Helen W Belding Geneva A Daland and Frederic Parker Jr[2] (Boston) on the basis of observation in 13 cases of monocytic and 8 of histiocytic leukemia The authors restrict the term monocytic leukemia to the Naegeli type and the term histiocytic leukemia to the Schilling type of monocytic leukemia Downey and others include both the Naegeli and the Schilling types under the common term monocytic leukemia Males predominated in the histiocytic group and females in the monocytic group Ages varied from 14 to 85 years in the monocytic and 5 months to 70 years in the histiocytic group All patients had either acute or subacute leukemia

Pulmonary infection and oral sepsis were the presenting complaints in most patients with monocytic leukemia Presenting complaints in most of the histiocytic group were nonspecific symptoms such as weakness anorexia weight loss of lymphadenopathy oral or pulmonary infections occurred in only a few Infections were not closely related to granulocytopenia Severe infection unresponsive to sulfonamides and penicillin was an important factor in the immediate cause of death in most patients with monocytic leukemia and a contributory cause in less than half the histiocytic group

Hemorrhagic phenomena not directly related to thrombocytopenia occurred more commonly in the monocytic group Although in general spleen and lymph node enlargement was greater in the histiocytic group there were no physical findings helpful in diagnosis

The degree of anemia tended to be greater and nucleated red cells were more common and numerous in the peripheral blood of the monocytic group Marked thrombocytopenia

(2) Ca 8 37 52 M Apr 1955

Experimental evidence links the lymphoid system to antibody production The wide spectrum of antibodies encountered in infectious mononucleosis appears in association with the characteristic monocytoid cell of lymphocytic origin and is sometimes the pathogenic mechanism for frank hemolytic anemia The disappearance of the unusual lymphocytic population in such cases is followed by spontaneous disappearance of the hemolytic syndrome

All 24 patients had pallor and icterus rarely severe and all but one had well defined splenomegaly Hepatomegaly was present in 20 Lymphadenopathy was marked in eight patients in the leukemia group slight and generalized in seven slight and localized in two and absent in three Two lymphosarcoma patients had moderate generalized lymphadenopathy and two patients had none Anemia was present in all patients erythrocyte counts varying from 860 000 to 3 300 000 All but four patients had a persistent elevation of the reticulocyte count Platelet counts tended to be slightly low Large foci of regenerating normoblasts with lymphocytic infiltration were seen in the bone marrow in many cases of leukemia and seemed to indicate the presence of hemolytic anemia This dual proliferation was seen in one case of lymphosarcoma Complete replacement of bone marrow by lymphocytes was present in three patients with leukemia without reticulocyte elevation Serum bilirubin levels varied from 0 9 to 9 mg /100 cc (average 2 8 mg) and most bilirubin was of the indirect reacting type Elevated fecal urobilinogen was a constant finding The direct Coombs test was positive in the 20 cases in which it was done Circulating hemagglutinins were present in 11 of 19 patients tested Therefore eight had fixed antibody but no circulating antibody Hemolysins were not demonstrable in any patients

Control of the hemolytic process will frequently restore the patient to a reasonable semblance of good health Control of the lymphocytic proliferation especially in chronic lymphocytic leukemia may be carried out by x ray therapy The newer chemotherapeutic agents particularly triethyleneamelamine are often very useful but may initiate or precipitate exaggerated hemolysis Thus far no agent displays ability to combat both processes To a limited extent

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(2) C 8 237 252 M Ap 1955

was present in all cases of histiocytic leukemia and in nine of monocytic leukemia A moderate platelet decrease was noted in two cases of monocytic leukemia Patients in the monocytic group tended to have much higher leukocyte counts than those in the histiocytic group in whom leukopenia was frequent Leukocyte counts tended to rise during the course of monocytic leukemia and remain static or fall in histiocytic leukemia Myelocytes were more numerous in monocytic leukemia Eosinophils and basophils were not increased or abnormal in either group An absolute lymphocytosis was present in slightly over 50% of the monocytic cases and in only one case of histiocytic leukemia The peripheral monocytes were normal or low in the histiocytic group and represented practically all the cells in some patients with monocytic leukemia Differentiation of a histiocyte and a monocyte may be difficult Monocytes are peroxidase positive and histiocytes peroxidase negative Monoblasts may give a negative peroxidase reaction

[The distinction between the two types of leukemia requires careful study of characteristic blood cells which are illustrated in the original article Infiltrative lesions of the skin such as those described in the following article are especially suggestive of histiocytic (Schilling type monocytic) leukemia —Ed]

Critical Study of Monocytic Leukemias is presented by R Degos B Ossipowski and H Baranger[3] (Paris) Monocytic leukemia takes at least two forms a leukemic type with malignant reticuloendotheliosis and lymphomonocytic leukemia In the former monocytes originate directly from reticuloendothelial hyperplasia without involvement of other cellular series In the latter lymphoid metaplasia is coupled with intense reticular and monocytic hyperplasia and metaplasia The two processes are parallel though there may be alternate discharges of lymphocytes and monocytes A large amount of reticular and histioid tissue in the skin explains the frequency of cutaneous manifestations in these leukemias

CASE 1—Man 70 was hospitalized one month after appearance of small purplish widely disseminated skin nodules (Fig 74) There was no itching fever mucous membrane involvement or change in general health Splenomegaly and adenopathy were present The general state deteriorated progressively after admission Biopsy of a skin nodule showed infiltration of the dermis and hypodermis by abnormal reticular cells (essentially monocytes) Apparently un

(3) Pr méd. 62 144 1445 O t 27 1954

affected skin showed exactly the same changes but to lesser degree On the first examinations the blood was almost normal but later white cell count showed 56% monocytic cells There was a pre dominance (56%) of large abnormal cells in the marrow inter pretable as hemocytoblastic or reticular cells [or histiocytes in the

Fg 74—Sk od l C 1 (C rt y f D g R t l P se méd. 6 144 1445 O t 27 1954)

terminology of the preceding article—Ed] (Fig 75) Death oc curred in one month after hectic fever weakness and weight loss

Some would consider this a case of myeloblastic leukemia (Naegeli) but the authors believe that a reactional cuta neous process secondary to myeloblastic or hemocytoblastic leukemia would scarcely create such severe disturbances in the reticular series Also the skin lesions preceded inva

sion of the blood by monocytoid cells These facts support a diagnosis of malignant reticuloendotheliosis with mono cytic leukemia (Schilling)

CASE 2 —Woman 40 had mucosal lesions in the pharynx which progressed to the buccal and lingual mucosa finally an ulcerated vegetative lesion appeared on the lower lip There was no spleno-



F g 75 —My l gram C e I h w ng num ous h mocyt bl t (C rte y of Deg R t l P méd 62 1442 1445 Oct 27 1954)

megaly or adenopathy The blood contained 67% typical monocytes (not stained by benzidine) A myelogram showed 73% large baso philic cells Monoblastic and monocytic leukemia was diagnosed Transfusions cortisone and antibiotics caused regression of the mucous membrane lesions and disappearance of anemia but monocytes persisted in the blood and the marrow became more mono blastic

This case exemplifies the most authentic (Naegeli) type of monocytic leukemia The abnormal blood cells were frank ly monocytic and marrow cells appeared to be both mono

blastic and reticular Burgeoning mucosal lesions are per haps more typical in this leukemia

CASE 4—Man 74 was hospitalized for an apparently benign slowly progressing skin eruption of erythematous vesicular oozing plaques somewhat infiltrated which caused intense itching Hard painless inguinocrural and axillary lymph nodes were found A hemogram showed 4 030 000 red cells and 58 400 white cells 70% lymphoid and 10% monocytic Marrow study revealed 30% neutro philic myelocytes 34% lymphoid cells 5% monocytes and 14% histiomonocytic types Lymph node biopsy showed 41% abnormal nu cleolated reticular cells 39% shriveled lymphocytes 10% prolymphocytes and 10% lymphoblasts Histiomonocytic hyperplasia with some lymphocytic infiltration was seen on skin biopsy Later hemo *grams revealed alternating proportions of lymphocytic and monocytic* elements After radiation therapy the skin lesions improved clinical ly and the blood showed suppression of lymphoid cells and stimula tion of monocytic elements One count revealed 60% monocytoids The patient died four months after admission following a recrudes cence of skin lesions

This case is an example of lymphomonocytic leukemia Alternate discharge of lymphocytes and monocytes and histiomonocytic hyperplasia of the skin with some lympho cytes indicated two parallel malignant processes one his tiomonocytic the other lymphoid

[Excellent illustrations and a text concerned with morphologic dis tinctions that some may find too difficult to make—Ed.]

Prognosis for Survival in Chronic Granulocytic and Lymphocytic Leukemia In an analysis of statistical meth ods Harold Tivey[4] (Univ of Oregon) found that distribu tion of survival times of patients with chronic lymphocytic or granulocytic leukemia after therapy or for total dura tion follows asymmetrical curves badly skewed but the logarithms of survival time after either therapy or onset approximate normal distribution A simplified maximum likelihood estimation method could be used to calculate logarithmic mean standard error and standard deviation These numbers represent the data completely and permit statistically valid comparisons of results of different investi gators

These technics were used to analyze the total survival from onset of symptoms to death in 32 series from the liter ature totaling 1 978 patients with lymphocytic or granulo cytic leukemia Fourteen series (651 patients) of known sur vival after therapy were similarly analyzed No differ

(4) Gen 1 72 68 93 J ly 1954

ence was demonstrated between survival prospects of patients with lymphocytic and patients with granulocytic leukemia either after onset or after treatment

Half of such patients will die in 1 6 years after beginning therapy or 2 65 years after onset of clinical symptoms The 95% confidence range of this estimate is 2 55 2 75 years Survival seven years after onset is 10% over 15 years about 1%

These technics were applied to 58 patients with lymphocytic and granulocytic leukemia treated only with titrated regularly spaced P^{32} or total body roentgen irradiation 28 are still living the newest patient of the series has been observed two years Maximum likelihood analysis predicts that 50% will have died by 4 8 years after onset of symptoms (95% confidence range 3 5-6 8 years) Probability that the difference between 4 8 and 2 7 years the 50% point for all data in the literature is due to chance alone is less than 1 in 1 000 If all 58 patients were dead January 1 1952 the first 50% would have survived 3 1 years Total effects of all improvements in both general medical care and specific therapy for leukemia have significantly improved the prognosis for survival of the present day patient treated by P^{32} or roentgen irradiation over that of the combined experience reported in the past 25 years

These results emphasize the need for continued research in therapy Median survival time of all white persons in the United States of the same age as patients studied when compared with predicted survival time indicates that approximately 20% of patients with leukemia will live less than one tenth their median survival time and 10% may live their median survival Fifty per cent of treated patients will live at least a quarter of the expectation for half of all white persons of their age The patient with chronic leukemia has a relatively good prognosis in comparison with that of cardiovascular disease or some of the more common malignant diseases [and he will benefit most from presently available therapy if it is carried out by or under the supervision of a physician who takes greater satisfaction in being a good doctor than in being a specialist —Ed]

Clinical Management of Leukemias is discussed by Joseph H Burchenal[5] (Cornell Univ) In leukemia the marrow is

(5) Ca c r R s 14 615 6 4 Octobe 1954

invaded by neoplastic cells which may arise from myeloid erythroid or megakarocytic elements normal cells are replaced with production of a variety of symptoms Lack of polymorphonuclear leukocytes leads to increased susceptibility to infections particularly pyogenic ones Lack of adequate red cells and hemoglobin diminishes oxygen transport and causes symptoms of anemia Platelet deficiency causes a hemorrhagic diathesis

Unfortunately in leukemia there is no known *qualitative* difference between normal and neoplastic cells to be exploited by chemotherapy nor can host resistance be relied on to aid in destroying leukemic cells Chemotherapy is based on *quantitative* differences in nutritional requirements of normal and leukemic cells particularly in acute leukemias With all agents used in treatment of leukemia the margin between therapeutic dose and toxicity is small

Arsenic has been used for chronic myelocytic leukemia since 1865 but it may produce pronounced nausea and vomiting Urethane (3 Gm daily by mouth for about 30 days) produces satisfactory remissions Nitrogen mustard in a total dose of 0 4/mg /kg body weight intravenously will cause remissions often lasting six months but triethylene melamine (TEM) (2 5 5 mg orally for two consecutive days each week until the white count is normal) or myleran (4-6 mg daily) followed by maintenance doses provides better control The purine antagonist 6-mercaptopurine (2 5 mg /kg orally) produces and maintains good remissions in a high percentage of patients

In chronic lymphocytic leukemia nitrogen mustards are useful but TEM is the drug of choice the dosage being approximately half that used for chronic myelocytic leukemia Urethane may also be of some value ACTH and cortisone have been found useful particularly when thrombocytopenia or hemolytic anemia is also present [See article by Rosenthal *et al* p 317 —Ed]

In acute leukemias aminopterin (0 25 0 5 mg) and a methopterin (2 5 5 mg) daily by mouth are used most commonly Children resistant to cortisone or 6-mercaptopurine may still be expected to respond to antifolics 6-Mercaptopurine will produce remissions in patients resistant to a methopterin or cortisone and in those responding first to mercaptopurine and later showing resistance a

methopterin or cortisone will often produce remissions 6 Mercaptopurine appears to be beneficial in monocytic leukemia and to be almost as effective in leukemias with high or low total leukocyte counts It also has considerable value in adults Corticosteroids produce remissions in 50 70% of children with acute leukemia and in a smaller percentage of young adults and are frequently active in patients in whom resistance to mercaptopurine or a methopterin develops In patients over 30 however they are rarely effective

Folic acid antagonists purine antagonists and hormones are all usually employed eventually in a given patient and

SURVIVAL TIME IN CHILDREN WITH ACUTE LEUKEMIA

	No P tients	1 Yr or Lo ger %
No treatment	218	5
Cortisone a methopterin	154	29
a Methopterin cortisone and 6-mercaptopurine	49	52

none can be called the best agent In deciding which to use first the following plan is helpful If a patient is acutely ill he is started on cortisone by mouth or ACTH by constant intravenous drip Once remission is apparent or the acute emergency has passed antimetabolite therapy with either a methopterin or 6 mercaptopurine may be started If patient is not too acutely ill antimetabolites are tried initially If the total white cell count is over 50 000 or the patient over age 10 6 mercaptopurine is preferable to a methopterin It is best to persist with one class of antimetabolite shifting to the other when resistance appears and holding hormones in reserve for uncontrolled exacerbations

Lack of cross resistance between folic acid antagonists purine antagonists and steroids has been exploited in treatment (table) Of the untreated children 50% survived less than 3 9 months those who had cortisone and a methopterin 8 9 months and in a series receiving all three agents over 12 months

The future hope of controlling leukemia lies in chemotherapy but until something more than quantitative differences are discovered between normal and leukemic cells it is doubtful whether any single agent will be sufficiently

specific to control the disease The an wer may be combination therapy By synthesizing screening and evaluating clinically alone and in combination analogues of biochemical reaction products efficacy of chemotherapy of leukemia should be brought to a level comparable to that of infectious disease

[This is a clear and authoritative statement of principles and practice of chemotherapy as of 1954 The author does not deny the present utility of ionizing radiation in chronic leukemias but believes that chemotherapy is as satisfactory and holds a greater promise for the future It is of interest that Osgood has reported survivals of over a year in patients with acute leukemia treated with cortisone and P[32] —Ed]

Effect of Triethylene Thiophosphoramide in Treatment of Leukemia and Certain Lymphomas in Infants and Children Nathan J Smith Salvator Rosello and Harry Shay[6] (Temple Univ) treated 21 patients aged 15 and under with thio TEPA in saline (10 mg /cc) given intramuscularly or intravenously and in two cases also orally Daily doses of 2 10 mg were used depending on hematologic and clinical findings Diseases treated were acute leukemia (12) differentiated myelocytic leukemia (3) lympho arcoma (5) and Hodgkin s disease (1) Diagnosis was confirmed by clinical evaluation peripheral blood smears and aspiration biopsy of bone marrow with lymph node biopsies in patients with lymphosarcoma and Hodgkin s disease Daily blood studies and periodic marrow studies were made during treatment

In cases of acute leukemia the authors were unable to tell whether the immature cells which had completely replaced the normal marrow were of lymphoid or myeloid origin Two patients had a short period of clinical and hematologic improvement after therapy In the rest clinical improvement with decrease in size of lymph nodes spleen and liver lasted two to five days and was followed by serious bleeding or overwhelming sepsis and death in a few days Decrease in dosage or administration of cortisone or cysteine hydrochloride was not helpful

Patients with lymphosarcoma had lymph node enlargement but little if any involvement of bone marrow Therapy resulted in prompt clinical improvement and rapid reduction in size of lymph nodes In three patients the effect was of relatively short duration and they did not respond to sub

(6) J Ped t. 46 493 505 M y 1955

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Cortisone a methopterin	154	29
a Methopterin cortisone and 6 mercaptopurine	49	52

none can be called the best agent In deciding which to use first the following plan is helpful If a patient is acutely ill he is started on cortisone by mouth or ACTH by constant intravenous drip Once remission is apparent or the acute emergency has passed, antimetabolite therapy with either a methopterin or 6 mercaptopurine may be started If patient is not too acutely ill antimetabolites are tried initially If the total white cell count is over 50 000 or the patient over age 10 6 mercaptopurine is preferable to a methopterin It is best to persist with one class of antimetabolite shifting to the other when resistance appears and holding hormones in reserve for uncontrolled exacerbations

Lack of cross resistance between folic acid antagonists purine antagonists and steroids has been exploited in treatment (table) Of the untreated children 50% survived less than 3 9 months those who had cortisone and a methopterin 8 9 months and in a series receiving all three agents over 12 months

The future hope of controlling leukemia lies in chemotherapy but until something more than quantitative differences are discovered between normal and leukemic cells it is doubtful whether any single agent will be sufficiently

count A new course was deferred until symptoms re turned regardless of the leukocyte rise Symptoms usually returned in 5 18 months With maintenance therapy an at tempt was made to reduce the leukocyte count to 10 000 20 000/cu mm and maintain it The dosage required var ied from 0 5 to 6 mg daily

Symptoms were rapidly relieved the hemoglobin level rose steadily and splenic regression was equal to but slower than with radiotherapy No side effects occurred Thrombocytopenia occurred only once since doses exceed ing 0 06 mg /kg body weight have been avoided The re sponse to the second courses was similar to the first re sponse although relapse occurred earlier

With standard doses the leukocyte count was approxi mately halved monthly When myleran was topped imma ture forms usually reappeared in the blood within six months although one patient had maintained a normal leukocyte count for nearly four years Although the leuko cyte count is a sensitive index of dosage the hemoglobin level is a more valuable and constant guide to the efficiency of myleran [i e whether the patient as well as his labora tory data are being benefited—Ed] Leukocyte response with maintenance therapy varied with the dose and no at tempt was made to obtain a further leukocyte fall when the hemoglobin increase was satisfactory Patients not respond ing adequately to radiotherapy showed good response to myleran Resistance to myleran developed in three patients on maintenance therapy Most patients require maintenance therapy after the second course of interrupted therapy

Myleran appears to be safe dependable and capable of producing prolonged remissions without side effects in prop er dosage and is therefore superior to most medications Al though experience is limited it would appear to be a satis factory substitute for radiotherapy

Myleran in Treatment of Chronic Myeloid Leukemia was used in 43 cases by R Klima J Beyreder and E Herzog[8] (Vienna) All patients reacted satisfactorily partly by com plete remission of leukocytosis and partly by a compensating regeneration of red blood cells and complete regression of splenomegaly In late cases remission was often not com

(8) W kl W h sch 66 682 685 S pt. 3 1954

sequent doses death followed bone marrow failure and leukemia The course was less acute and more prolonged in the other two who were older

Of the patients with well differentiated myelogenous leukemia one who was treated while in terminal myeloblastic crisis failed to respond one showed temporary response with death after 27 months of illness and one had been maintained on therapy free of symptoms for 20 months The patient with Hodgkin s disease responded well to oral therapy for two weeks after which he was lost to follow up

Triethylene thiophosphoramide appears to resemble other ethylenimine derivatives except for an antineoplastic effect This was noted in three patients in the present series with disappearance of leukocytosis lymphadenopathy and splenomegaly and normal blood cell production manifested by an increase in erythrocytes and blood platelets The drug is contraindicated in acute leukemias and the acute leukemic phase of lymphosarcoma Since toxic marrow depression may occur with injudicious use strict observation of the patient is necessary during treatment

Myleran in Chronic Myeloid Leukemia D A G Galton and M Till[7] (London) report results of a four year trial with myleran in chronic myeloid leukemia during which 31 patients were treated Some had received other medications The drug was given orally in 0 5 mg and 2 mg tablets Short intensive courses of 100 150 mg given in one to six days were first used but were discontinued because of severe bone marrow depression The standard adult dose has since been 0 06 mg /kg body weight daily An initial loading dose was found to be unnecessary The first 20 patients received one or more courses of myleran with 6 eventually receiving maintenance therapy Eight died within a year of the only course seven having received short intensive therapy The other 11 patients received only maintenance therapy given after an initial period on standard dosage

With standard dosage a course lasted three to seven months The duration was determined by clinical and hematologic improvement and rate of fall of the leukocyte

(7) Lancet 1 425-430 Feb 26 1955

and a barbiturate and chlorpromazine are repeated at mid night if the patient is awake If additional medication is necessary chlorpromazine may be given parenterally Seri ous consequences can be prevented usually by spacing cours es at least six weeks apart and similarly after irradiation Generally the beneficial effect lasts longer than six weeks *Action of TEM is slower so nitrogen mustard is preferred* for patients with toxic symptoms TEM is valuable in maintenance therapy because it can be given orally and without sedation or hospitalization Oral dose is 0 05 0 4 mg /kg i e 5 25 mg in a single course Not over 5 mg

SUMMARY OF CHEMOTHERAPY OF LEUKEMIA AND RELATED DISORDERS

Disease	X ra p	M stard Congeners		Myleran	Ure-thane	Folic Acid Antagonists	Cortisone ACTH	MP
		HN	TEM					
Hodgk	++++	++++	+++	0	0	C	±	C
Chro c lymphocy t l k m	+++	++	+++	0	0	C	±	C
Lymphosarcoma	+++	++	++	0	0	C	±	C
Reticul m cell sa coma	++	++	+	0	0	C	0	C
Ch my locy t leuk m	+++	+	+	++++	++	C	C	+
Acut l k m —								
lymph bl tic	C	C	C	0	0	++++	++++	++
my l bl t	C	C	C	0	0	+++	C	++
mo ocyt	C	C	C	0	0	+	C	+

4 pl se eq l ff t and p f bl 3 pl ffect 2 plu mod rat ly ffect 1 pl l ghtly ff t ± met m eff t e 0 in ffect and C on tra d t d

should be given in one day It is best given with water on an empty stomach more consistent absorption prob ably is achieved if 2 Gm sodium bicarbonate is given simultaneously It may also be given intravenously 0 05 0 15 mg /kg in a course Tolerance may decrease neces sitating caution in repeated courses

Some patients with chronic lymphocytic leukemia are par ticularly sensitive to TEM and can be maintained in good condition for long periods with this drug Only 2 5 mg orally may suffice Larger doses should be used only after evaluation of the patient s sensitivity Its effects in lympho sarcoma differ widely but small doses may produce im provement In some cases serious hemopoietic depression has developed Little can be expected in reticulum cell sar coma

For hemolytic anemia complicating Hodgkin s disease and

plete and the terminal increase of myeloblasts was not inhibited nor influenced The drug was well tolerated and kidney complications were not observed

In a patient with polycythemia a leukemoid leukocytic picture and splenic tumor the leukocyte count became normal and erythrocytes decreased A patient with splenomegaly and a leukemoid blood picture definitely improved

Myleran is an effective specific cytostatic in chronic leukemia surpassing all other cytostatic drugs used heretofore without their toxic effects It is as effective as roentgen irradiation and seems to be effective in cases refractory to roentgen irradiation A particular advantage is the possibility of ambulatory treatment [Of course irradiation can also be given to ambulatory patients —Ed]

The best method of administration is not definitely known Longer observation will be necessary to establish whether 8 10 mg daily or protracted treatment with 2-4 mg produces a more lasting effect In individual cases the latter dose given as long as 10 months has produced definite remissions

The leukocyte count is not so important an indication for this therapy as spleen size and general condition Erythrocyte and hemoglobin levels are a good index for treatment since after a decline is evident it almost always continues

Chemotherapy of Leukemia Hodgkin s Disease and Related Disorders is classified (table) and discussed by M M Wintrobe G E Cartwright Phaedon Fessas Arthur Haut and S J Altman[9] (Univ of Utah) on the basis of 10 years experience

In Hodgkin s disease useful drugs in decreasing order of effectiveness and value are nitrogen mustard triethylene melamine (TEM) triethylene phosphoramine (TEPA) and diethylene phosphoramine (DEPA) and beta naphthyl di 2 chloroethylamine (R48) The value of nitrogen mustard is clear single dose of 0 2 mg /kg body weight is followed the next day by 0 2 0 4 mg /kg depending on the total dose elected (rarely more than 0 6 mg /kg) It is usually given in the evening with 25 mg chlorpromazine at four hour intervals beginning about noon the same day Nembutal 0 1 Gm is also given with the mustard (8 p m)

(9) An I t Med 41 447-464 S pt mbe 1954

with multiple myeloma Horace H Zinneman and Wendell H Hall[1] (Univ of Minnesota) observed 13 with bacterial pneumonia exclusive of terminal bouts 10 of these had a total of 44 recurrent episodes For this reason it appeared desirable to investigate the immunologic response of such patients

A very feeble or absent precipitin response was obtained in 10 patients with multiple myeloma without pneumonia after subcutaneous immunization with 0 08 ml each of pneu mococcus polysaccharides types I and II as compared to normal adult controls In six of seven patients with mye loma challenged by subcutaneous administration of 0 10 ml of a 1 100 dilution of polysaccharide fraction of Brucella abortus specific agglutinins failed to develop All seven normal controls responded with agglutinin titers of 1 80 1 320 The one patient with adequate brucella agglutinin titer had normal serum protein Over all response of the same seven patients to typhoid paratyphoid vaccine was very weak Three developed no agglutinins and had defi nitely abnormal serum globulins

Humoral and cellular immune factors are the major nat ural defenses against pneumococcic invasion Clinical re sistance to pneumonia can be correlated with antibodies to type specific polysaccharides The pneumonia of the 13 pa tients responded promptly to conventional antibiotic thera py yet there were recurrences caused by the same organ ism These 13 patients showed no clear relation between serum protein abnormality and frequency or severity of re current pneumonias but all with definitely abnormal pro tein patterns had recurrent bouts whereas one with a nor mal protein pattern had but one episode Immunochemical abnormalities of serum globulins of the 10 patients without pneumonia may have accounted for the poor antibody re sponse to experimental antigenic challenges

Recurrent pneumonia in patients with multiple myeloma and in those with agammaglobulinemia is immunologically similar Although gamma globulins of the two conditions are opposite quantitatively there is a profound reduction of immunologically active serum globulins In both bacte rial infections tend to recur despite prompt response to antibiotics

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(1) An I t M d 41 1152 1163 Dec mbe 1954

chronic lymphocytic leukemia cortisone is more useful than nitrogen mustard and has largely replaced splenectomy in the authors' cases

In chronic myelocytic leukemia myleran is most effective In oral doses of 2 8 mg daily usually 4-6 mg it causes sharp fall in leukocyte count usually well pronounced after three weeks and subjective improvement Remission in 11 treated cases lasted 2 12 months after stopping therapy As many as four repeated courses have been effective Bone marrow hypoplasia was observed only once after 476 mg myleran in three months Ease of administration and low cost make it the preferred agent in this disease Urethane 1-4 Gm a day by mouth is less consistently useful and may cause gastrointestinal symptoms

In acute lymphoblastic leukemia the authors use cortisone initially replacing it with a methopterin after complete remission The daily dose required to obtain remission is often 150 mg but sometimes 300 mg even in children given in three or four divided doses Potassium chloride 3-6 Gm and a low salt diet (1 2 Gm NaCl) daily are also given Despite hypercorticism no serious ill effects have been encountered Cortisone is reduced gradually in one to two weeks and a methopterin is substituted 1 25 5 mg/day orally dose is titrated according to clinical condition In acute myeloblastic or monoblastic leukemia choice lies between a folic acid antagonist and the antimetabolite 6-mercaptopurine though with any agent the outlook is poor Over all results with 6-mercaptopurine have not been as good as those with antifolic acid agents or hormones in acute leukemia in children but it may have a place when resistance to other agents has developed It deserves thorough trial in adults and patients of all ages with myeloblastic leukemia

These agents do not displace irradiation which is as valuable as any drug in the conditions discussed except acute leukemia Most effective management is judicious use of the whole available therapeutic armamentarium

↓ The next two articles explain the basis of the association between myeloma and pneumococcus infections that clinicians have sometimes suspected—and others have denied —Ed.

Recurrent Pneumonia in Multiple Myeloma and Some Observations on Immunologic Pesponse Amon atients

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Humoral and cellular immune factors are the major natural defenses against pneumococcic invasion Clinical resistance to pneumonia can be correlated with antibodies to type specific polysaccharides The pneumonia of the 13 patients responded promptly to conventional antibiotic therapy yet there were recurrences caused by the same organism These 13 patients showed no clear relation between serum protein abnormality and frequency or severity of recurrent pneumonias but all with definitely abnormal protein patterns had recurrent bouts whereas one with a normal protein pattern had but one episode Immunochemical abnormalities of serum globulins of the 10 patients without pneumonia may have accounted for the poor antibody response to experimental antigenic challenges

Recurrent pneumonia in patients with multiple myeloma and in those with agammaglobulinemia is immunologically similar Although gamma globulins of the two conditions are opposite quantitatively there is a profound reduction of immunologically active serum globulins In both bacterial infections tend to recur despite prompt response to antibiotics

(1) A 1 t M d 41 1152 1163 Dec mber 1954

Observations on Antibody Content of Blood in Patients with Multiple Myeloma Occasionally patients with multiple myeloma manifest striking susceptibility to pneumonia One patient in the present study had had 3 attacks of acute lobar pneumonia in four months another had had 10 attacks of acute pneumonia in four years Herman A Lawson C A Stuart Alton M Paull Arthur M Phillips and Roswell W Phillips[2] (Providence R I) studied nine patients (table) Four showed no antibodies including blood group antibodies two on initial examination and two subsequently Although some antibodies were present in serum of the other five who had only single examinations only Case 3 showed a normal content Case 4 had a deficiency of antibodies isoagglutinins were present in unusually low titer and amboceptor was absent Cases 5 6 and 8 were definitely abnormal isoagglutinins being deficient or absent and few other antibodies being found Not every normal person has all the antibodies included in this study but complete absence of all antibodies or lack of appropriate isohemagglutinins was observed only in patients with myelomatosis It is likely that further tests in the five examined only once would show progressive decrease and ultimately complete or nearly complete disappearance of circulating antibodies Amboceptor was not detectable at any time in serum of these nine patients though it was present in 97% of controls None showed agglutinins for salmonella O and

TITERS OF ANTIBODIES IN NINE PATIENTS WITH MYELOMATOSIS

Case	Blood Group	Agglutinin for			Lysin for 3564 OP	Amboceptor
		3 64 OP	A Cells	B Cell		
1	A	0		0	0	0
2	A	0		0	0	0
3	O	0	1 160	1 80	1 160	0
4	O	1 10	1 5	1 10	1 40	0
5	O	1 10	0	1 20	1 80	0
6	O	0	0	0	1 40	0
7	B	0	0		0	0
8	A	0		0	1 20	0
9	O	0	0	0	0	0
Av for normal controls		1 135	1 90	1 40	1 65	1 390

(2) N w Engla d J Med 252 11 18 Jan. 6 1955

H 901 although these antibodies were found in 84% of controls

Analysis of serum proteins by filter paper electrophoresis was done in five patients all of whom showed deficiency of antibodies which were absent in four Four showed a high peak of gamma globulin and the fifth (Case 9) a tall peak representing the so called M component with absence of gamma globulin Case 9 was nevertheless remarkably free from infection in contrast to patients with agammaglobulinemia (without myeloma) and especially to Case 1 with pronounced increase in gamma globulin and frequent episodes of pneumonia over 2½ years Both showed lack of antibodies

Serums of four patients with multiple myeloma were compared with control serums for their effect on phagocytic action of polymorphonuclear cells against Micrococcus pyogenes var aureus Three patients including Case 1 showed weaker phagocytic action than the controls whereas serum of Case 2 failed completely to promote phagocytosis Control serums demonstrated normal phagocytic action

The immunologic abnormality demonstrated in multiple myeloma is considered to be the result of abnormal function of the malignant plasma cells whereby deranged protein synthesis results in production of abnormal proteins at the expense of normal proteins including antibody protein The electrophoretic peaks of gamma globulin thus do not indicate an increase of functional antibody

↓ *It is* reassuring *to find in the next article that Waldenstrom s* macroglobulinemia is part of the spectrum of associations between plasma cells and anomalous plasma proteins that range from lack of plasma cells with agammaglobulinemia to hypergammaglobulinemia of various kinds associated with patholog c increases of plasma cells—or are they lymphocytes that look like plasma cells?—Ed

Waldenstrom s Macroglobulinemia which usually afflicts older men is described by E Mandema[3] (Groningen The Netherlands) The patient complains first of fatigue which increases progressively and then becomes sick pale and dyspneic on exertion Mucosal hemorrhages especially from the nose or gums occur Weight decreases and some patients have acrocyanosis Painless lymph nodes are common Sometimes the liver and spleen are moderately enlarged Retinal hemorrhages may occur The course may be

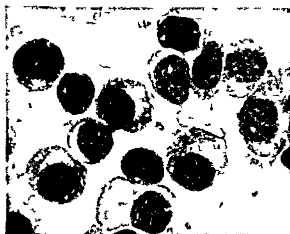
(3) N d t tijdsch gen k 98 2109 2118 J l 31 1954

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1	A	0		0	0	0
2	A	0		0	0	0
3	O	0	1 160	1 80	1 160	0
4	O	1 10	1 5	1 10	1 40	0
5	O	1 10	0	1 20	1 80	0
6	O	0	0	0	1 40	0
7	B	0	0		0	0
8	A	0		0	1 20	0
9	O	0	0	0	0	0
Av for normal controls		1 135	1 90	1 40	1 65	1 390

(2) New England J Med 252 13 18 Jan. 6 1955



F g 76 —Ma w m (bt d by t t my f f m) N t dı t t t s tion to pl m ll typ d ben gn ppe f latt M y Gru w ld G emsa stain ×1350 (C rt y f M d m E N d l tıjd h g k 98 2109 118 J ly 31 1954)

MULTIPLE MYELOMA (25 CASES) — MACROGLOBULI EM (10 CASES)

PA N (SKELETON)
PATH FRACTURE
TUMOR FORMATION
RAD OLOG CAL SIGNS
BENCE JONES PROT
EDEMA
PALP LIVER AND SPLEEN
BONEMARROW PUN TURE DIFFICULT
? LESIONS FUNDUS OC
ACROCYA OSIS
EPISTAXIS
E LARGED LYM HNODES
LYMP O D PLASMACELLS
MALE

X OSTEO OROS S ONLY
⊏ ⊐ POS N 4 OUT OF 5 CASES

F g 77 —D fferen ın f q y f p ın pal ympt m ın lt ple m l m d mac ogl bul m (Court y f M d ma E N derl t ıd h gen k 98 2109 2118 J ly 31 1954)

cally ın two ın which the marrow yielded no normal cells The cells were somewhat larger than lymphocytes The nu clear structure corresponded ın many respects with that of normal plasma cells (Fig 76) The nucleus was eccentric as ın the plasma cell but ın most cells the quantity of cyto

prolonged over many years Patients are too ill to work yet not sick enough to be bedfast Anemia increases progressively especially as hemorrhages become more frequent Cachexia and severe anemia eventually lead to death

Some lymph nodes show small lymphoid cells and plasma cells though no abnormalities are found in others Marrow often is difficult to obtain by bone puncture It contains the same lymphocyte like cells frequently not definitely distinguishable from small lymphoid reticulocytes and varying numbers of plasma cells Sedimentation rate is often greatly increased and changes in blood proteins are similar to those in multiple myeloma Usually there are no discernible x ray changes but sometimes a diffuse indistinct osteoporosis is seen Although thrombocytes are normal or moderately decreased clot retraction is practically nil so that it is difficult to obtain serum Sometimes the serum or plasma becomes a gel on cooling but reliquefies on warming At other times serum or plasma separates into a clear and normally fluid top layer and a turbid sometimes extremely viscous bottom layer This phenomenon disappears when the tube is warmed Using ultracentrifugation Waldenstrom and Pedersen demonstrated in plasma or serum globulin with a high sedimentation constant and high molecular weight from which the name macroglobulinemia is derived Macroglobulins sometimes behave like cryoglobulins but cryoglobulins seldom have a high molecular weight

A similar syndrome but with signs of central nervous system involvement (radiculitis myelitis and encephalitis) was described by Bing and Neel in 1936 The cerebral membrane and blood vessels are infiltrated by lymphoid and plasma cells The protein content in the cerebrospinal fluid is increased Predominant symptoms are sometimes neurologic (including pareses) and sometimes psychic

Mandema observed three cases and added a fourth from the records The symptoms corresponded with previous descriptions of macroglobulinemia The first patient also had neurologic (and psychic?) symptoms In two cases in which determinations could be made macroglobulins were demonstrated

Cytologic findings in these cases were striking espe

and plasma cell precursors The abnormal proteins were globulins of unusual electrophoretic homogeneity which was especially impressive when globulins were present in high concentration Electrophoretic mobility varied from gamma to nearly that of beta protein In three abnormal protein in the serum decreased as disease activity was suppressed by therapy

Whether the anomalous components are proteins with an abnormal structure or normal constituents present in unusual concentrations and of apparent homogeneity is uncertain That these proteins have a unique significance to the malignant state is unclear but their presence only in diseases characterized by abnormal proliferation of plasma cells or lymphoid tissue suggests that they are a product of perverted protein synthesis associated with malignant growth of these cells

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VASCULAR AND THROMBOCYTOPENIC PURPURAS

Functional Pathology of Platelets According to S Van Creveld[5] (Univ of Amsterdam) at least six factors have been isolated from platelets 1 accelerates conversion of prothrombin into thrombin 2 promotes conversion of fibrinogen into fibrin under the influence of thrombin 3 is responsible for neutralization of heparin and participation of platelets in formation of blood thromboplastin 4 is a vasoconstrictor called serotonin 5 is a fibrinogen like substance which can be coagulated with thrombin and contributes to instability of Ac globulin and 6 has antifibrinolytic activity In addition platelets contain a retractozyme e g a factor concerned in clot retraction attached to the so called platelet hyalomer other enzymes and at least in the rabbit histamine Platelets also are able to form white thrombi

Factor 1 corresponds to the platelet accelerator globulin of Ware Fahey and Seegers Whether delayed conversion of prothrombin into thrombin in thrombocytopenia is due to absence or diminution of factor 1 or is related to reduction

(5) A ta h mat 12 2 9 237 1954

plasm was small Numerous cells had two nuclei a frequent finding in plasma cells

All symptoms observed in macroglobulinemia are also seen in multiple myeloma but signs sometimes seen in the latter such as bone pain and roentgenologically visible nodules have not been observed in macroglobulinemia Frequency of certain symptoms in the two conditions varies considerably (Fig 77) Mandema finds the term macroglobulinemia objectionable because macroglobulins apparently are not the causative factor (as Waldenstrom evidently believed originally) He believes that macroglobulinemia should be regarded as a variant of multiple myeloma

Serum Proteins in Leukemia Of 35 patients studied by R Wayne Rundles Evelyn V Coonrad and Tulio Arends[4] (Duke Univ) 15 had chronic lymphocytic 8 subleukemic lymphocytic, 7 chronic granulocytic and 5 acute or subacute leukemia Specimens obtained before and after therapy were studied by Tiselius electrophoresis Total serum protein concentrations were determined by the biuret method and standardized by bovine serum albumin

In patients with chronic lymphocytic leukemia with mild or no constitutional symptoms serum protein findings were predominantly normal In those seriously ill with chronic lymphocytic leukemia or with chronic granulocytic acute or subacute leukemia hypoalbuminemia and increase in different globulin constituents occurred frequently They were proportionate to severity and progression of the disease and seemed to be nonspecific reactions

Irradiation and triethylene melamine (TEM) generally produced no adverse changes in serum proteins Excessive doses of TEM causing severe bone marrow depression resulted in hypoproteinemia involving all serum components Reduction in serum albumin and rise in gamma globulin concentration were observed in four patients given urethane for several months suggesting an adverse effect on hepatic function

Anomalous components were found in the serums of four of the eight patients with subleukemic lymphocytic leukemia one with atypical lymphocytic leukemia and one with myelogenous leukemia and proliferation of erythroid

(4) Am J Med. 16 842 855 Jun 1954

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(5) A ta h mat 12 229 237 1954

of factor 3 needs further study Nothing is known about the functional pathology of factor 2

Some patients with thrombocytopenia display a close relation between number of platelets and ability of the blood to neutralize heparin A hemorrhagic diathesis also occurs in which factor 3 is lacking from platelets but platelet count is not decreased (thrombopathia hemophilica) In six cases observed only factor 3 was lacking all other known clotting factors were present in the blood Lack of factor 3 due to thrombocytopenia of different origin (essential thrombocytopenia and various secondary thrombocytopenias) means decreased ability to neutralize heparin in vitro and may also signify increased tendency to hyperheparinemia which may contribute to the hemorrhagic disorder Essential for thromboplastin formation are antihemophilic factor factor 3 of the platelets and the Christmas factor or plasma thromboplastin component (PTC) Before diagnosis of thrombopathia hemophilica (defect of platelet factor 3) can be made hemophilia Christmas disease and PTA deficiency must be excluded (defective plasma factors)

Presence of a retractozyme in platelets explains their role in clot retraction and abnormality of retraction in thrombocytopenia and thrombopathia The platelet vasoconstrictor is released when agglutination and lysis of platelets occur after lesion of the intima Bleeding time and capillary fragility also are related to platelet levels

Treatment of thrombocytopenia with suspensions of thrombocytes is difficult because these cells are extremely labile when removed from plasma Transfusions in children with primary and secondary thrombocytopenia and thrombopathia with specially prepared fresh platelet suspensions retaining 60 75% of the thrombocytes originally present in the blood affected platelet count clotting time and clot retraction usually for two to four days In some cases of thrombocytopenia platelet counts rose to normal In thrombopathia clotting disturbances caused by lack of factor 3 temporarily disappeared In leukemia with thrombopenia and in aplastic anemia with thrombopenia results were less striking

[Not only are the effects of platelet transfusions transient but anti platelet antibodies soon develop —Ed]

Prognosis in Idiopathic Thrombocytopenic Purpura of Childhood based on 43 cases, is discussed b[illegible] Kom

rower and G H Watson[6] (Royal Manchester Children's Hosp) All patients were 16 or under and had platelet counts below 120 000/cu mm in all but three counts fell below 100 000 The disease was classified as acute in 24 who died or recovered completely within six months chronic (ill over six months) in 12 indeterminate probably acute in 5 unclassified in 2

In 12 of the acute cases symptoms were severe i e extensive ecchymoses severe epistaxis or spontaneous bleeding from other sites Six died three of uncontrollable hemorrhage and three of intracranial bleeding Eleven of the 18 survivors recovered within six weeks and all but 1 in three months Only one relapsed after platelets had risen above 200 000 The only serious nonfatal complication occurred in a boy with probably acute disease who had an intracranial hemorrhage during the third week of illness Thrombocytopenia was later corrected by splenectomy but he remained blind and hemiplegic

Among chronic cases nine had symptoms over two years and one over one year Two were cured by splenectomy after 6½ and 12 months Severity of symptoms varied greatly Platelet counts during periods of bruising were 100 000 200 000 but during remissions rose to over 200 000 Relapses did sometimes follow after platelet counts rose to over 200 000 After splenectomy three of five patients had immediate permanent cure symptoms and thrombocytopenia ceased about two years after operation in one and the last improved steadily for 15 months

A well defined onset indicated an acute condition with a relatively short course i e under six months Presence of infection during three weeks preceding purpura indicated sudden onset Spontaneous bleeding from multiple sites and extensive ecchymoses occurred before fatal hemorrhages and indicated grave prognosis Splenomegaly was equally uncommon in acute and chronic cases Neither blood nor marrow eosinophilia was correlated with course or response to splenectomy but peripheral eosinophils were absent in fatal cases Platelet levels in the first three weeks could not be correlated with severity of symptoms and had no prognostic significance

During the first month of illness risk of death or serious

[6] Arch D Childhood 29 50 506 Dec mb 1954

complications is appreciable Most survivors will have complete remission in six months or less and no fatal bleeding occurs in the others Risk of splenectomy in acute stages is great and ACTH or cortisone should be used during the first month in the first six months splenectomy should be avoided if symptoms are clearing even if platelets remain low Later decision to remove the spleen should depend on degree of disability produced and not on fear of sudden disastrous hemorrhage which is a relatively slight risk

Quinidine Induced Thrombocytopenic Purpura Report of 14th Case and Review of Clinical and Experimental Studies are presented by Louis Weisfune Paul W Spear and Martin Sass[7] (Brooklyn)

Woman 70 hospitalized because of diffuse ecchymoses for 10 days had been medicating herself with thiomerin for hypertension aminophylline phenobarbital and papaverine for vague abdominal complaints quinidine for supraventricular tachycardia and sulfonamides for infections The liver descended one fingerbreadth below the right costal margin there was no lymphadenopathy and no splenomegaly Laboratory data were red blood cells 2 750 000 hemoglobin 6 5 Gm mean corpuscular volume 80/cu μ mean corpuscular hemoglobin concentration 25% white blood cells 13 800 reticulocytes 4 5% platelets 11 000 coagulation time 7 minutes Rumpel Leede test strongly positive bleeding time over 60 minutes clot retraction none in 24 hours stool guaiac 4+ direct Coombs test positive and indirect negative cold agglutinins negative blood urea nitrogen 24 mg urinalysis negative An ECG showed supraventricular tachycardia The bone marrow was normally cellular Megakaryocytes were reduced and nonproductive of platelets There was moderate normoblastic hyperplasia Granulopoiesis was orderly

All drugs were discontinued. Platelet level returned to normal four days after a blood transfusion Bleeding time clot retraction and the Rumpel Leede phenomenon returned to normal Petechiae and ecchymoses gradually subsided

Eight days after entry quinine was prescribed for a persistent arthritic complaint but instead 0 2 Gm quinidine was given in error Within 12 hours diffuse petechiae and ecchymoses developed over the entire body and in the oral mucous membranes Platelets were absent on the peripheral blood film and bleeding time clot retraction and Rumpel Leede reaction were markedly abnormal Quinidine was continued and the platelet count gradually rose to normal by the seventh day

An in vitro platelet agglutinin was demonstrated on incubation of

(7) Am J Med 83 414-422 September 1954

normal platelets sensitized plasma and quinidine Omission of quinidine uniformly resulted in a negative agglutination reaction The antibody was a panagglutinin since all human platelets so tested were agglutinated Heterologous rabbit platelets could not be substituted for human platelets Substitution of quinine the levorotary isomer of quinidine failed to produce any agglutination Optimal concentration of quinidine was 5 mg / 100 cc

This case emphasizes the importance of detecting specific sensitizing agents by in vivo and in vitro methods in determining the cause of the idiopathic or allergic types of thrombocytopenic purpura particularly when a variety of drugs has been administered Observations by others indicate that quinidine has induced thrombopenia in four days during its initial use In 11 instances of sensitization a test dose has caused a precipitous fall of platelets within hours Patch tests have been negative Recognition of the offending drug and not splenectomy is the important measure

Compounds E and F and ACTH in Management of Idiopathic Thrombocytopenic Purpura Chris J D Zarafonetis William A Steiger and Sarah K Cary[8] (Temple Univ) report results in 11 cases A rise in platelets was not uniformly noted Three patients had little or no platelet response to cortisone (two) and compound F (one) Splenectomy appears to have effected a cure in one the second had suboptimal platelet remission after operation and the third had an ephemeral rise in platelets and has since had marked thrombocytopenia (10 months after operation) A fourth patient with a satisfactory but temporary platelet remissions on cortisone and compound F also appears to have been cured by splenectomy In seven patients adequate platelet remissions resulted during each course of cortisone or compound F Two appear to be cured and further follow up is planned on two others All four received only a single course of compound F orally The other three have had a total of eight courses of steroid therapy Although platelet remissions were induced on each occasion gradual relapse occurred after cessation of therapy Splenectomy may ultimately be done

When clinical bleeding was present it was promptly controlled by steroid therapy Capillary resistance as measured by the Rumpel Leede test uniformly improved within a few

(8) Am J M Sc. 228 1 15 J ly 1954

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(7) Am J Med. 88 414-422 Sept mber 1954

disease was 54 hours to 10 years All but two patients had fever and all but five neurologic manifestations—disturbances of consciousness motor paralysis seizures and rarely evidence of spinal cord or peripheral nerve damage Splenectomy was done on eight patients with improvement in one ACTH or cortisone was given to eight without significant benefit Heparin appeared ineffective Hemorrhagic manifestations were present in 39 cases Lymphadenopathy was infrequent hepatomegaly was present in 13 and splenomegaly in 16

The red cell count was usually below 4 000 000 the lowest count was 1 080 000 Hemoglobin content varied from 18 to 78% of normal The anemia was usually normochromic normocytic and the red cells generally showed marked anisocytosis and poikilocytosis Reticulocyte counts were elevated in 28 of 29 cases Peripheral smears showed nucleated red cells (25% of cases) and polychromatophilia Spherocytes were seen in six cases [Many patients have increased osmotic fragility but usually a negative Coombs reaction —Ed] The leukocyte count was above 12 000 in 27 cases and above 30 000 in 5 Leukopenia developed in three cases A leukemoid reaction occurred in 38 Severe thrombocytopenia was the rule counts usually ranging from 10 000 to 100 000 The bone marrow showed erythroid hyperplasia in 14 of 22 cases granulocytic shift to the left in 4 erythroid decrease in 1 and erythrophagocytosis in 2 Urine examination in 44 cases showed albuminuria in 30 red cells in 35 and casts in 14 Urine urobilinogen was elevated in 8 of 17 cases and fecal urobilinogen in all of 4 tested Cerebrospinal fluid was normal in 12 of 23 cases and showed increased protein in the others with a slight increase in lymphocytes in a few The sedimentation rate was usually normal or slightly elevated Blood urea nitrogen or nonprotein nitrogen tested in 31 cases was increased in 21

The pathognomonic histologic finding is a homogeneous eosinophilic material partially or completely occluding arterioles capillaries and rarely venules throughout the body Most authors agree that these thrombi are partially or entirely platelets The organs usually involved are the heart brain adrenal cortex lymph nodes kidney liver and spleen

The cause of the thrombocytopenia is obscure Studies

days These effects were noted during therapy with cortisone (eight courses orally two intramuscularly) compound F (eight courses orally) and ACTH (two courses intramuscularly) Compound F parenterally was ineffective in one patient but oral administration to the same subject induced a remission on two occasions Improvement in capillary resistance was sustained as long as therapy was continued even in the absence of platelet increase L E cell preparations were negative Positive reactions to Coombs tests were obtained in three cases Two patients had repeatedly positive serologic reactions for syphilis but the treponemal immobilization test was negative [a well recognized serologic prelude to clinical lupus erythematosus —Ed]

Steroid therapy is ideal for emergency management of idiopathic thrombocytopenic purpura and for preoperative preparation for splenectomy Properly controlled treatment with cortisone hydrocortisone or ACTH initiated at the time of diagnosis constitutes a more conservative approach than watchful waiting for a spontaneous remission The latter can no longer be justified as bleeding into a vital area may occur

Thrombohemolytic Thrombocytopenic Purpura is the term suggested by Edward Adelson Edward J Heitzman and John F Fennessey[9] (Boston) for a condition characterized by an unusual triad—hemolytic anemia thrombocytopenic purpura and multiple hyaline thrombi throughout the small vessels of the body—and presently called thrombotic thrombocytopenic purpura The authors review data on 46 cases from the literature and add 3 new cases 2 of which were diagnosed ante mortem

The 49 patients were aged 9½ 69 two thirds being between 10 and 40 60% were females Nine patients had a history of rheumatic fever or rheumatoid arthritis three renal disease two thrombophlebitis and two positive serologic reactions for syphilis Other past illnesses were leg ulcers discoid lupus pleuritis Raynaud s phenomenon recurrent eclampsia and tuberculosis Many had histories of allergic tendency Prodromas usually upper respiratory infections were present in 12 patients Total duration of the

(9) A M A A h I t M d 94 42 60 J ly 1954

on the upper trunk arms face and mucous membranes of the mouth and nose The percentage of those afflicted corre sponded with that usually reported One patient had spleno megaly

Pulmonary fistulas present in two patients and probably present in another have been commonly associated with hereditary hemorrhagic telangiectasia but the true incidence is unknown The incidence of hereditary telangiectasia in patients has been reported as 50 60% In this series the pul monary fistulas caused no symptoms in two patients and dyspnea palpitation dizziness and chest pain in one The latter a woman aged 53 had cyanosis finger clubbing pulmonary murmurs and compensatory polycythemia and died during an attack of dyspnea and cyanosis

Fluoroscopy with the Valsalva and Muller procedures is helpful in diagnosis of pulmonary fistulas and angiocardio grams are usually conclusive Large fistulas should be re moved Smaller ones should be removed if they increase in size or cause symptoms such as polycythemia Even when asymptomatic small fistulas may cause serious bleeding and brain abscess

Estrogens in females and estrogen androgen tablets in males may help to prevent epistaxis probably because they cause a thicker more moist nasal mucosa This effect was noted in one patient in this study (a man aged 45) in whom epistaxes were frequent and severe

Investigation of Large Family Affected with Willebrand s Disease is reported by J C W Macfarlane and M J Simp kiss (Hosp for Sick Children London) In this condition first described by von Willebrand and colleagues in 1926 tendency to bleed occurs oftenest in childhood and appears as recurrent epistaxis bruising bleeding following dental operations gastrointestinal bleeding and prolonged bleed ing from injury and operation sites Menorrhagia and post partum hemorrhage may be severe in women Hemarthro sis has been reported and rarely hemorrhage into deep tissues and organs The sexes are equally affected and the family history usually shows inheritance to be of simple dominant type though some authors have reported apparent sex linkage The disease appears to be cyclic and to decrease

(2) A h D Ch ldh od 29 483 487 Dec mbe 1954

in the authors cases seemed to substantiate the theory of increased platelet destruction (Fig 78) Normally platelets survive three to five days Despite clear evidence of a hemolytic mechanism in the production of anemia the authors were unable to demonstrate red cell autoantibodies or isoantibodies in their patients Coombs reactions were negative

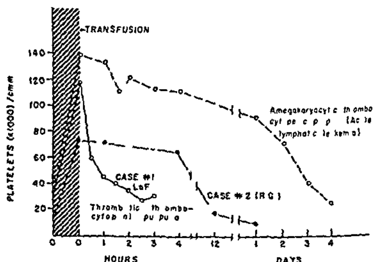


Fig 78 —Platelet survival in two of authors cases and patient with secondary thrombocytopenia (Courtesy of Adelson E et al A M A Arch Int Med 94 42 60 July 1954)

The disease is considered to represent a hypersensitivity state involving red blood cell platelet megakaryocyte and cell wall

[This condition must always be considered in the differential diagnosis of thrombocytopenia. A possible explanation of the anemia and thrombocytopenia would be that the multiple partial or complete vascular occlusions convert many tissues into filter beds for the circulating elements in this way resembling the spleen —Ed]

Hereditary Hemorrhagic Telangiectasia Report of Pulmonary Arteriovenous Fistulas in Mother and Son Medical (Hormonal) and Surgical Therapy of This Disease Edward C Heyde[1] (Vancouver Wash) reports the occurrence of signs of hereditary hemorrhagic telangiectasia in 7 of 36 members of a family and the probable occurrence in 4 others The lesions are true vascular spiders usually

(1) Ann. Int M d 41 1042 1054 November 1954

The only abnormal laboratory finding was prolonged bleeding time varying from 7 minutes 30 seconds to several hours and not related to severity of the disease In 12 of 18 cases bleeding time was normal on occasions and prolonged on others A study of nailbed capillaries in two members of the family showed a defect of retraction

Since it is an almost universal finding that patients with this abnormality bleed after some dental extractions and not after others surgical intervention without capillary hemorrhage should be possible whenever the bleeding time is within normal limits

[ACTH or cortisone would be expected to be of value but observations with these agents are not reported here —Ed]

Intravascular Microembolic Carcinomatosis as Cause of Purpura Report of Case Associated with Focal Histologic Lesions in the Nervous System The simultaneous occurrence of purpura and carcinomatosis is uncommon In most reported cases the primary growth was in the stomach usually associated with widespread bone metastases only occasionally was there no thrombocytopenia W T Smith and A G W Whitfield[3] report a case of intravascular carcinomatosis not demonstrable during life presenting as purpura without thrombocytopenia

Woman 49 7½ years after radical mastectomy for carcinoma had purpuric manifestations followed by hematuria Urologic studies and the hemogram revealed nothing significant Hematuria and bruising continued and after several months she was hospitalized No evidence of malignancy could be found Except for anemia and a few red cells polymorphonuclears and coliform bacilli in the urine laboratory findings were essentially negative Six days after admission she died suddenly of cerebral hemorrhage

At autopsy only trivial macroscopic evidence of metastases was found but histologic studies showed tumor emboli in the skin and glomerular capillaries The terminal hemorrhage may have resulted from rupture of small degenerative blood vessels Emboli elsewhere in the body unusual distribution of effused blood and absence of cerebrovascular disease excluded coincident spontaneous hemorrhage Petechial hemorrhages microscopic softenings and focal demyelination in the cerebral cortex resembled experimental embolic lesions Changes in the cerebellum and peripheral nerves were focal as sociated with carcinomatous emboli and did not include systematized tract degeneration

The picture was remarkably similar to that seen in the platelet thrombosis syndrome

(3) B t J Ca 8 97 106 M h 19 4

in severity with increasing age Laboratory studies show a prolonged bleeding time with normal platelet count coagulation time, prothrombin time prothrombin consumption and clot retraction Abnormal capillary morphology and function have been reported and may be the cause

The family studied included 38 females and 26 males of five generations of whom 10 females and 11 males are or were affected 33 were examined and in 11 affected members a complete investigation with current hematologic methods was made The seeming preponderance of males is well within chance distribution Hematologic confirmation was obtained in 18 of the 21 affected members (2 were dead and 1 was unavailable for examination) Nine were 5 years old or less when the disease first became manifest 4 were 6 10 2 were in their teens and 2 showed the first evidence at 21 and 23 Of 43 unaffected members 16 were still under 10

The bleeding conforms to the classic picture Sixteen have recurrent epistaxis as the main symptom 11 have prolonged and uncontrollable bleeding following some dental extractions 7 bruise easily and 3 have had recurring gastrointestinal hemorrhages due to confirmed or suspected peptic ulcer Of seven postmenarchial females only one complains of menorrhagia and that is doubtful five have experienced no bleeding complication at parturition in 24 births Severity of bleeding varies considerably one patient is as yet symptomless (bleeding times over 10 minutes) and one has been disabled throughout his youth because of recurrent debilitating epistaxis and later severe hematemeses and intestinal hemorrhages, presumably from a duodenal ulcer In 10 of the 21 bleeding causes but transient embarrassment and in 6 it requires short bed rest Three require prolonged rest on occasion and in two transfusions have been necessary at times

Bleeding is periodic there is apparently no precipitating factor and the pattern is completely unpredictable varying from a few days of scanty bleeding separated by many months of freedom therefrom to severe bleeding for several weeks with but short remissions and relatively short free periods However if the affliction is severe at the beginning it remains severe

plasma rabbit serum and adsorbed rabbit serum) The factor was assayed (Quick test) by degree of correction of stored plasma (poor in labile factor) expressed as clotting time in seconds

In tests for antithrombin eluates of paper segments of human plasma proteins were mixed with thrombin residual thrombin was plotted as clotting time in minutes after addition of fibrinogen In two tests (human serum and oxalated human plasma) this thrombin inactivating prop

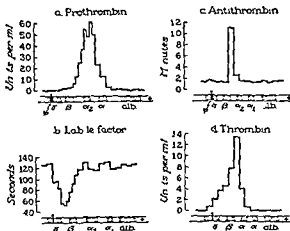


Fig 79—Electrophoretic localization of blood clotting factors Arrows indicate line of application of serum or plasma (Courtesy of Owen C A Jr and Mhenze B F J Appl Ph 16 696-700 May 1954)

erty was between beta globulin and alpha globulin (Fig 79 c)

The addition of 5 000 units of commercial powdered bovine thrombin to 2 ml human serum resulted in a smeared electrophoretic pattern Further dilution of this mixture with serum led to fairly clearcut patterns in two tests in both of which thrombin (measured by the addition of fibrinogen and expressed as units of thrombin/milliliter was detected between the beta globulin and alpha globulin zones (Fig 79 d) where antithrombin was also found

Fibrinogen was usually visible at the line of application of plasma to the paper (ϕ in Fig 79 a and c) In two tests

It was concluded that the patient died from the effects of intravascular tumor emboli that had not resulted in macroscopic metastases that carcinoma cells may have existed in the blood stream commensally since the original operation and that similar embolization may play some part in malignant purpura

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COAGULATION DEFECTS

Application of Paper Electrophoresis to Separation of Blood Clotting Factors is described by Charles A Owen Jr and Bernard F McKenzie[4] (Mayo Clinic and Found)

METHOD —Serum and plasma proteins were dispersed in barbiturate buffer at pH 8 6 While still wet the paper was processed as follows A central lengthwise strip 1 cm wide was cut out, dried and stained with bromophenol blue to establish the location of the bands of protein for the entire paper Lateral strips were cut into 1 cm bands and eluted by 0 9% solution of sodium chloride (for serum) or by 0 1 M sodium oxalate in 9 parts of saline (for plasma) These saline or oxalated saline eluates were then used in the clotting tests

In tests with five samples of human serum four of oxalated canine plasma and single samples of oxalated human plasma thrombin defibrinated oxalated human plasma canine serum thrombin defibrinated oxalated canine plasma and rabbit serum the stable conversion factor was within the beta globulin zone No difference was detectable between the location of this factor in serum and plasma

In two tests one with oxalated canine plasma and one with canine plasma fortified with Seegers purified bovine prothrombin prothrombin assayed by the two stage method and recorded in units/milliliter coincided with alpha globulin (Fig 79 *a*)

Six tests of the labile factor revealed some variability (Fig 79 *b*) In two peak activity was at the anodal limit of the gamma globulin area (thrombin defibrinated canine plasma and calcium orthophosphate adsorbed rabbit plasma) In four it lay between the beta globulin and the gamma globulin zone (oxalated human plasma oxalated canine

(4) J Appl Physiol 6 696 700 May 1954

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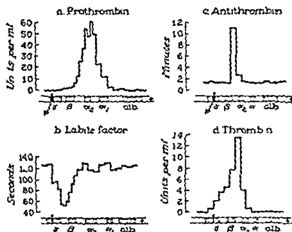


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Fibrinogen was usually visible at the line of application of plasma to the paper (ø in Fig 79 *a* and *c*) In two tests

on oxalated human plasma flecks of fibrin were seen in eluates from this zone after the addition of thrombin

Such distribution of serum or plasma proteins by electrophoresis affords a means of localizing biologic activities if methods of detection are sufficiently precise and if activities are stable enough to withstand the procedure It is clear that not all proteins are localized with the albumin alpha globulin beta globulin or gamma globulin zones some protein is localized between these zones

The most mobile factor studied was prothrombin which tended to concentrate with $alpha_2$ globulin Electrophoretic separation of prothrombin in $alpha_2$ globulin and its stable conversion factor in beta globulin was sufficiently sharp to confirm the concept that these are separate entities

Congenital Afibrinogenemia *Study of Some Basic Aspects of Coagulation* in three subjects is reported by Benjamin Alexander Robert Goldstein Lester Rich Anne G Le Bolloc h Louis K Diamond and Wayne Borges[5] (Harvard Med School) Such subjects possessing only one abnormality of the coagulation system and that in its final stage require minimal manipulation of the blood in vitro

Boy 4½ and another boy 5 and his sister 1½ had had repeated spontaneous and post traumatic hemorrhages into skin muscles joints and loose tissues Parents of the siblings were first cousins but there was no familial history of hemorrhagic disease *No abnormalities could be detected in the blood of any of the parents* The children s bloods remained fluid indefinitely in glass clotting tubes and failed to clot on addition of thrombin or thromboplastin Their plasmas exhibited no precipitate when heated at 52 C and orthodox methods showed no fibrinogen *Newer immunochemical tests on two showed no more than 1 2 mg /100 ml fibrinogen or fibrinogen like material No other hematologic or clinical abnormalities were found* Infusion of normal blood plasma or plasma fraction I repeatedly restored normal hemostasis and rectified the clotting defect

Studies on the bloods of these patients permit portrayal of the coagulation sequence exclusive of the fibrinogen fibrin mechanism After the blood is exposed to glass earliest detectable are morphologic change in platelets and their progressive agglutination and lysis Within three minutes some platelets became swollen showed tails and cobwebs some clumping was also evident At five minutes many

(5) Blood 9 843 865 September 1954

platelets vanished At eight minutes the platelets appeared coalesced into large clumps and a few faint shreds (fibrin?) appeared in the plasma In close parallel perhaps simultaneously plasma antihemophilic activity originally normal disappears rapidly Ac globulin becomes activated and is rapidly consumed while serum prothrombin conversion accelerator is elaborated from its precursor These changes are well along before detectable amounts of prothrombin have disappeared Prothrombin consumption proceeds at normal velocity or slightly faster Thrombin addition to afibrinogenemic plasma induces platelet agglutination but this does not occur when thrombin is mixed with platelets alone Natural antithrombic activity of afibrinogenemic plasma is normal The heparin co factor of antithrombic activity is demonstrable Quantitative data relating the one stage prothrombin time with the fibrinogen concentration were obtained in the author s patients

Although hemorrhage is prominent in afibrinogenemia coagulable blood is not essential for some degree of hemostasis The authors patients had long intervals free from hemorrhage Significance for hemostasis of a normal vascular tree must not be minimized but agglutination of platelets their adhesion to endothelial surfaces and their lysis are important in afibrinogenemia these functions seem unimpaired

The relation between fibrinogen concentration and plasma prothrombin time has practical interest If plasma prothrombin time is normal fibrinogen level must be over *100 mg/100 ml Below this prothrombin time progressively* rises with the curve correlating the two which permits a rough calculation of fibrinogen concentration from prothrombin time if prothrombin and prothrombin conversion factors are normal and if fibrinogen level is low enough to give a considerably elevated prothrombin time At such levels orthodox methods of measuring plasma fibrinogen may be unreliable

Congenital Hypoprothrombinemic States usually due to lack of a single clotting factor offer natural physiologic experiments Repeated study of patients from six families permitted Armand J Quick Anthony V Pisciotta and Clara V Hussey[6] (Marquette Univ) to collect data on course

[6] I t Med 95 2 14 J ry 1955

diagnosis treatment hereditary pattern and nature of various prothrombin factors

Four distinct clinical entities of congenital origin exhibit prolonged one stage prothrombin time Two are due to low free prothrombin concentration in type I the cause appears to be an inadequate capacity to produce prothrombin while in type II the mechanism which fixes the ratio of free to total prothrombin is altered The third is caused by lack of an accessory factor variously designated as stable proconvertin factor VII SPCA or co thromboplastin The fourth is due to labile factor (proaccelerin factor V or Ac globulin) deficiency

The two accessory factors are significant but puzzling Prothrombin consumption is poor when labile factor is deficient but normal when stable factor is lacking suggesting that the former acts earlier in conversion of prothrombin to thrombin The labile factor is normal in both types of true hypoprothrombinemia and in stable factor deficiency Total prothrombin is normal in all but type I hypoprothrombinemia One exception is that stable factor appears to be somewhat low in type II hypoprothrombinemia Prothrombin time of stable factor deficiency can be corrected by addition of normal plasma whereas in type II deficiency it remains prolonged The Y factor which the authors believe determines the amount of prothrombin is normal in all but type II hypoprothrombinemia

Hereditary transmission though not established in all four types seems reasonably certain In stable factor deficiency a bleeder inherits two defective genes i e he is homozygous If he marries a normal person none of his children will be bleeders but all will be heterozygous and will give the trait to half their children The unmodified test for prothrombin time readily detects the offspring with the defective trait they should not marry someone also heterozygous to this defect Although the trait is rare in one family both mother and father have it and their daughter received the defective gene from both parents Labile factor deficiency appears to have the same hereditary pattern That of hypoprothrombinemia type I is not known Only in type II is it probable that if a person has sufficient

depression of prothrombin to be a bleeder he will have chil dren who are bleeders

Vitamin K will not correct the prothrombin time except possibly in true hypoprothrombinemia in which natural vitamin K_1 sometimes has a slightly beneficial effect Only plasma or whole blood may temporarily elevate prothrombin sufficiently to effect hemostasis In labile factor deficiency blood must be fresh since the labile factor dis appears during storage whether transfusion of serum has advantages over plasma is not known but control of bleed ing with blood and serum in a patient with proved stable factor deficiency has been reported

Clinical Application of Simplified Serum Prothrombin Consumption Test is described by Leon N Sussman Ira B Cohen and Robert Gittler[7] (Beth Israel Hosp New York

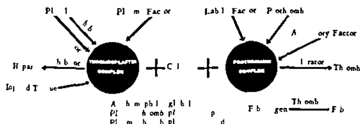


Fig 80—C rr t th e f blood oagulat on (C rt y f S m n L N et l J A M A 156 70 05 Oct 16 1954)

City) No single explanation for blood coagulation has been generally accepted practically all recent theories by Seeger Quick Owren and Ware are shown schematically in Figure 80)

In normal coagulation presence of excess thromboplastin complex leads to almost complete consumption of pro thrombin In vitro the *plasma* prothrombin time measures deficiencies of the prothrombin complex Serum obtained after this normal clot has formed contains little prothrom bin In contrast when coagulation abnormalities occur be cause of lack of thromboplastin prothrombin is not con sumed during clotting and serum will contain more pro thrombin Thus determination of *serum* prothrombin time

(7) J A M A 156 70 705 Oct. 16 1954

is in reality a quantitative measure of the original thromboplastin

The serum prothrombin consumption test described by Quick has not been commonly used because of its complicated technic. The simplified method for serum prothrombin time can easily be performed in any laboratory where plasma prothrombin determinations are done.

TECHNIC.—Blood to be tested is allowed to clot at room temperature. It is placed in a water bath at 37 C for one hour after clotting and centrifuged three minutes. The serum is separated and may be stored at 4 C for a maximum of 60 minutes before the test. Thromboplastin solution is prepared as for the plasma prothrombin test. Fibrinogen solution is prepared as directed by the manufacturer (to contain 300 mg fibrinogen/100 cc of 85% NaCl solution). Two cc of thromboplastin solution and 1 cc fibrinogen solution are mixed just before the test. Of the mixture (0.2 cc) is placed in a test tube in a water bath at 37 C for five minutes. The serum to be tested is warmed in the water bath at 37 C for five minutes. Serum (0.1 cc) is blown strongly into the thromboplastin fibrinogen mixture (timer should be started simultaneously) and clot formation time is determined as in the plasma prothrombin test. The test is interpreted as follows: time longer than 30 seconds normal; shorter than 20 seconds abnormal; between 20 and 30 seconds doubtful. Longer periods of incubation consume more prothrombin; shorter periods less.

Patients with thrombopenia, either primary or secondary, have consistently had short serum prothrombin times, indicating poor utilization of prothrombin. This means that lack of platelet "enzyme" results in thromboplastin deficiency, which in turn precludes normal utilization of plasma prothrombin; hence more prothrombin is found in the serum.

A single intravenous injection of 100 mg heparin prolonged clotting time from 10 to 90 minutes, while plasma prothrombin time increased from 13 to 16 seconds and serum prothrombin time fell from a normal of 34 seconds to 12 seconds. Undoubtedly heparin has multiple sites of action on coagulation, but these results indicate that its major action is on the thromboplastin complex. The antithrombin action of heparin probably prevents labilization of platelets as suggested by Quick. In contrast, drugs that produce hypoprothrombinemia, e.g., bishydroxycoumarin, have no effect on serum prothrombin consumption. Regardless of the initial lack of plasma prothrombin, residual

serum prothrombin will remain low and serum prothrombin time will be normal or prolonged

Clotting time as an index of correction of hemophilia defects has erroneously implied enzymatic action The prothrombin consumption test shows that the correction is quantitative and stoichiometric A mixture of 75% of hemophilic blood with 25% of normal blood shows a partial correction of abnormal prothrombin consumption this could be increased by a 50 50 mixture and further restored to normal by a 25 75 mixture Correction in thrombopenias was likewise quantitative

To evaluate the indictment that corticotropin and cortisone may be causative agents in thrombophlebitis several cases were studied No alteration in coagulation time (Lee White) plasma prothrombin time or serum prothrombin consumption time was observed

Study of platelet abnormalities both quantitative and qualitative is aided by this test Separation of the several functions of platelets permits a better understanding of their role in the coagulation mechanism Considerable more research is needed to explore fully the possibilities of the test and to understand the action of various drugs on the coagulation system

Relative Incidence of Antihemophilic Globulin (AHG) Plasma Thromboplastin Component (PTC) and Plasma Thromboplastin Antecedent (PTA) Deficiency Study of 55 Cases previously diagnosed simply as hemophilia is reported by Paul G Frick[8] (Univ of Minnesota) Until recently hemophilia was generally considered a single disease with a coagulation defect characterized by prolonged clotting time and decreased prothrombin consumption Description of hemophilia like conditions from which blood or plasma corrected the coagulation defect in other patients with presumed hemophilia made this assumption untenable Besides the classic hemophilia caused by a deficiency of antihemophilic globulin (AHG) adequate evidence exists for at least two additional conditions with similar clinical and laboratory features such as prolonged blood coagulation The first was called plasma thromboplastin

(8) J Lab & Cl M d 43 860 866 J 1954

component (PTC) deficiency by White and associates who found that PTC deficient plasma contains normal quantities of AHG The second was described by Rosenthal and colleagues as plasma thromboplastin antecedent (PTA) deficiency PTA deficient plasma corrected the clotting defect in AHG and PTC deficiency

In the design of special differential diagnostic tests the physicochemical properties of AHG PTC and PTA and their behavior during spontaneous coagulation of normal blood were applied AHG and PTA are not absorbed by $BaSO_4$ while PTC can be completely removed from normal oxalated plasma with this salt Normal serum contains PTC and PTA but is devoid of AHG hence the clotting defect in AHG deficiency can be restored to normal with normal $BaSO_4$ treated plasma but not with normal serum PTC deficiency is unaffected by normal $BaSO_4$ treated plasma but responds to normal serum PTA deficiency is corrected by normal $BaSO_4$ treated plasma and by normal serum Diagnosis of the single cases was based on ability or failure of normal $BaSO_4$ treated plasma and normal 48 hour old serum to correct abnormal clotting time and prothrombin consumption Such aged serum is free of thrombin and largely free of labile factor and prothrombin

Clotting defect in 45 patients was due to AHG deficiency 6 had PTC and 4 PTA deficiency Uniformly poor consumption of prothrombin in AHG PTC and PTA deficiency indicates that these factors are important during thromboplastin formation although the exact mechanism is unknown [See article by Sussman *et al* p 355—Ed]

AHG and PTC deficiency are indistinguishable clinically In both severity of hemorrhagic symptoms ranges from occasional hemorrhagic episodes to severe crippling after repeated hemarthroses The hereditary pattern in both is recessive and sex linked The present study confirms original description of PTA deficiency as a mild hemorrhagic diathesis occurring in both sexes though further data are needed to establish these characteristics as differential criteria

Principal therapy in all three types of hemophilia is transfusion of normal plasma or blood The effect of transfused plasma lasts much longer in PTC than in AHG deficiency

Normal serum is effective in PTC and inert in AHG deficiency The instability of AHG in normal plasma makes the giving of fresh plasma mandatory PTC is more stable on storage than AHG Cohn s fraction I is devoid of PTC AHG deficiency responds to Cohn s fraction I PTC deficiency remains unaffected

Plasma Thromboplastin Antecedent (PTA) Deficiency Clinical Coagulation Therapeutic and Hereditary Aspects of New Hemophilia Like Disease Robert L Rosenthal O Herman Dreskin and Nathan Rosenthal[9] previously reported PTA deficiency in two sisters and their maternal uncle All had moderately severe hemorrhagic disease with a blood coagulation disturbance resembling hemophilia They had normal amounts of antihemophilic globulin (AHG) and plasma thromboplastin component (PTC) or Christmas factor PTA differs from both AHG and PTC but closely resembles PTC Both PTA and PTC are unconsumed during coagulation present in serum and stable on storage Treatment of either normal plasma or serum with $BaSO_4$ or by Seitz filtration completely removes PTC but eliminates only slight to moderate amounts of PTA AHG is not removed by these measures Maximal PTA activity is in the 25 33% ammonium sulfate fraction of normal plasma AHG activity chiefly in the 0 25% and PTC activity in the 33 50%

The present study of 13 members comprising four generations of the original PTA deficient family showed that of 11 descendants of the parents of one and grandparents of the other two original patients 6 had either mild or marked PTA deficiency and 5 were normal This incidence of 55% falls close to the theoretical incidence of 50% to be expected with simple dominant inheritance The hereditary pattern of PTA deficiency differs from that of the sex linked recessive transmission of both AHG and PTC deficiencies Inheritance of PTA deficiency as an autosomal dominant trait plus mildness of its hemorrhagic syndrome indicates that it may become a frequent clotting defect It can be transmitted by either male or female to either male or female progeny making a 50% chance of transmission by the carrier who also has the disease It

(9) *Blood* 10 120-130 February 1955

is not known whether the defect can be transmitted by an asymptomatic carrier with no laboratory evidence of PTA deficiency

The disorder can occur in degrees varying from a severe form with prolonged clotting time and markedly abnormal heparin clotting time and prothrombin utilization as seen in the three original cases to a mild form with normal clotting time and slightly impaired prothrombin utilization Spontaneous bleeding is rare It has usually followed trauma or surgery whether a major operation or a tooth extraction Hemarthrosis and purpura have rarely been seen The PTA defect can be corrected therapeutically by giving stored plasma with the effect gradually disappearing in about a week

Familial Hemorrhagic Trait Associated with Deficiency of a Clot Promoting Fraction of Plasma Oscar D Ratnoff and Joan E Colopy[1] (Western Reserve Univ) report on three patients (two of them sisters) who had prolonged clotting time of shed venous blood without significant hemorrhagic traits The defect appeared to be familial with both sexes involved and could not be identified with any hematologic disorder The plasma in each case was deficient in a substance found in normal globulin which accelerated the clotting time of normal platelet deficient plasma A clot promoting factor was prepared from normal barium sulfate adsorbed heated serum which was neither thrombic nor thromboplastic and did not alter the rate of conversion of fibrinogen to fibrin by thrombin or of prothrombin to thrombin by tissue thromboplastin The active principle was separated from antihemophilic globulin (AHG) and plasma thromboplastin component (PTC) but not with certainty from plasma thromboplastic antecedent (PTA) Its effect seemed to be on the development of thromboplastic activity in shed blood It did not appear to contain any of the plasma components necessary for optimal thromboplastic activity

Woman 46 had a prolonged clotting time first noted 16 years previously when a salpingo oophorectomy was performed without incident after postponement for two hours because of the clotting defect. There was no history of abnormal bleeding and pregnancy appendectomy and tonsillectomy had been performed without inci-

(1) J Cl I t 34 602 613 Ap 1 1955

dent There were severe varices and a few tiny ecchymotic spots on the legs Platelet count clot retraction and bleeding time were normal The tourniquet test was equivocal Plasma contained 3 44 Gm albumin 0 40 Gm alpha globulin 0 68 Gm beta globulin 0 72 Gm gamma globulin and 0 35 Gm fibrinogen like material per 100 ml

[It will be important to ascertain whether plasma from PTA deficiency will correct the coagulation defect of these patients—Ed.]

Nature and Action of Circulating Anticoagulants which may develop in hemophilic patients after transfusion and in nonhemophilic persons were investigated by Cecil Hougie and Michael E Fearnley[2] (West London Hosp Med School) Over 18 cases associated with hemophilia and 19 without hemophilia have been reported

Two men 19 and 23 with hemophilia and a previously normal man 82 are added by the authors During and after an abdominal operation the third patient bled profusely and despite transfusion of 2 pt stored blood died the next day

The addition of 20 or 40% of each patient s oxalated plasma to normal plasma greatly increased the recalcification time of the latter In all three cases circulating anticoagulants inhibited formation of blood thromboplastin by preventing a time consuming reaction between antihemophilic globulin and serum Once this reaction had occurred addition of platelets even with a large excess of inhibitor resulted in full thromboplastin generation Patients platelets were active in thromboplastin generation when added to normal alumina treated plasma serum and calcium The circulating anticoagulants have no action on formed thromboplastin and so are not antithromboplastins but antithromboplastinogens *The anticoagulants* were all *nondialyzable* heat stable surviving at 70 C for 10 minutes and present in gamma and beta globulin fractions of both plasma and serum Results of precipitin tests were positive in a solution containing antihemophilic globulin

It is generally accepted that circulating anticoagulants found in hemophilic patients are antibodies the antigen being the antihemophilic globulin present in transfused blood or blood products Positive precipitin reactions to antihemophilic globulin in some recorded cases furnish the main experimental substantiation At present antihemophil

(2) A t h m t 1 110 1954

ic globulin cannot be obtained free from other proteins and it seems likely that these tests are not specific This opinion is supported by the positive precipitin reactions to an antihemophilic globulin solution in the nonhemophilic patient with a circulating anticoagulant in whom no evidence of immunization was found and who had never received a blood transfusion Administration of ACTH or cortisone did not prevent hemorrhagic manifestations nor alter the titer of the circulating anticoagulants in the two hemophilics

Fibrinogenopenia Complicating Pregnancy Clinical and Laboratory Studies One of the most dramatic complications of pregnancy is the hemorrhagic diathesis that may occur as a result of fibrinogen deficiency Dieckmann (1936) found fibrinogen concentrations below normal in 7 of 11 patients with abruptio placentae and in 3 the concentration was below 50 mg/100 cc Of 10 patients with fibrinogenopenia during pregnancy studied by Dudley P Jackson Robert C Hartmann and Trent Busby[3] (Johns Hopkins Univ) 7 had abruptio placentae The presence of mild hypertensive toxemia in only two suggests that there is no causal relation between toxemia and fibrinogenopenia None of the seven had afibrinogenemia but the fibrinogen depression was usually severe especially since values are normally elevated in pregnancy Thrombocytopenia was present in six patients and prothrombin deficiency in five No evidence of increased fibrinolysis was found in the plasma Vaginal delivery was done in five and cesarean section in two Hysterectomy was done on two patients All received multiple whole blood transfusions and two received a small amount of fibrinogen All patients survived and correction of the coagulation defect occurred after delivery

In one patient hypofibrinogenemia occurred in association with fetal death in utero and prolonged retention of the fetus No increased fibrinolytic activity was found in the patient s plasma Fetal death was thought to be associated with pyelitis in the sixth month of pregnancy No premature placental separation was demonstrated The patient was Rh positive and the coagulation defect was not due to blood incompatibility Vaginal delivery was spontaneous with rapid recovery

(3) O st & Gynec 5 223 247 M rch 1955

Hypofibrinogenemia occurred as a complication of amniotic fluid embolism in one case. Thrombocytopenia was not present. There was suggestive but not conclusive evidence of increased fibrinolytic activity of the patient's plasma. Excess bleeding did not occur, but the patient died in shock immediately after delivery.

Afibrinogenemia occurred as a complication of septic abortion in one case. The coagulation defect was afibrinogenemia, thrombocytopenia, prothrombin deficiency, and a reduction of plasma accelerator activity. There was no evidence of fibrinolytic activity of the patient's plasma, and no circulating anticoagulant was found. The patient died with massive hematemesis soon after admission.

In no case was there any definite evidence of fibrinolysis in the plasma. Apparent fragmentation and/or dissolution of the whole blood clot is a function of low fibrin content and not proof of fibrinolysis unless the original fibrinogen content of the blood is normal. Others have shown that placental extracts and amniotic fluid possess thromboplastic activity, and a pathway of possible entry of these substances into the maternal circulation has been demonstrated. The authors believe that this results in increased utilization of fibrinogen with subsequent fibrinogenopenia.

[This is an excellent and clinically well documented statement of the present status of this grave obstetric problem. Embolism with thromboplastic material rather than primary fibrinolysis is now the favored concept of etiology. In the following article, however, it seems easier to adopt the primary fibrinolytic concept to explain at least the second case as in the fourth case of the next succeeding article.—Ed.]

Two Cases of Afibrinogenemia in Field of Obstetrics and Gynecology are reported by E. Revelli and M. Cottafavi[4] (Univ. of Turin).

CASE 1.—In a primigravida, 27, an uncontrollable hemorrhage developed during forceps delivery in labor induced because of preeclampsia. The infant died and the uterus failed to contract. During hysterectomy, performed because of persistent hemorrhage and incoagulable blood, an infusion of 2,000 cc. blood and considerable physiologic saline was given. Bleeding continued through the night and the following day, during which 3,000 cc. blood, 800 cc. plasma, 100 cc. dry concentrated plasma, and 250 cc. glucose solution were given in addition to other medical treatment. Death occurred the following day despite another 950 cc. blood, 1,000 cc. plasma, and 1,000 cc. physiologic saline with intensive medical treatment. Autopsy showed severe hepatic change with acute necrosis. Fluid blood filled the abdominal cavity, and there was hemorrhagic infiltration

[4] 38:1255-1258, 1954.

of the abdominal wall All other organs were anemic and showed small serosal petechiae

Fibrinogen had almost disappeared from the blood (52 2-67 86 mg/100 cc) the day after operation A decrease in thromboplastin and fibrinolysis was evident the following day The terminal decrease in coagulation and prothrombin was attributed to hepatic failure

CASE 2—Woman 34 attempted abortion during the second month of pregnancy by introducing a concentrated solution and solid potassium permanganate into the vagina This produced intolerable burning and severe vaginal hemorrhage and the patient was admitted in a state of shock Despite vaginal tampons and infusion of enormous quantities of blood plasma and isotonic solution, hemorrhage persisted and vaginal surgery was done. Ligation of corroded arteries and manual counterpressure against the abdominal wall resulted in almost complete hemostasis Hemorrhage soon recurred and hysterectomy was performed During the two operations 2,500 cc blood was given followed by 3 000 postoperatively because of shock Bleeding 20 hours after operation required 1 200 cc blood and oxygen therapy The patient s condition was serious for 36 hours then hemorrhage gradually subsided and cure was complete within a month

This case was classified as fibrinogen deficiency on clinical grounds though this was not proved The primary cause was probably erosion by potassium permanganate of two cervicovaginal arterioles and numerous smaller vessels at the posterior fornix Shock may have aggravated the fibrinolytic process or the caustic may have liberated fibrinolytic enzymes from the uterus

Transfusion and hysterectomy may save the patient though they were unsuccessful in preventing death in the first case Presence or absence of irreversible parenchymal lesions determines the success or failure of this treatment

Abnormal Plasma Proteolytic Activity Diagnosis and Treatment are discussed by Edward V Z Scott W Frank Matthews Charles E Butterworth Jr and Walter B Frommeyer Jr[5] (Med College of Alabama) The current concept of plasma proteolytic enzymes embodies a balanced system consisting of the active enzyme plasmin its precursor plasminogen and its inhibitor antiplasmin Plasminogen and plasmin reside in the globulin and antiplasmin in the albumin fraction of plasma proteins Plasmin can digest fibrinogen prothrombin plasma and serum prothrombin accessory substances casein gelatin and other proteins as well as fibrin Its free circulation in blood can

(5) S rg Gy ec & Obst 99 679-688 Dec mber 1954

seriously disturb coagulation resulting in severe hemorrhage Ensuing shock may then alter hemostasis through endothelial hypoxia causing widespread vascular damage and further loss of blood and plasma thereby augmenting shock Without interruption of this cycle death from hemorrhage and shock may ensue

The authors describe five cases in which there was alarming hemorrhage due to abnormal proteolytic activity In the first it was believed that plasminemia developed during prostatectomy Bleeding diminished after routine treatment of shock including whole blood transfusions The blood of the second patient demonstrated complete failure of the clotting mechanism after prostatectomy although there was only moderate bleeding during operation Administration of whole blood and serum albumin did not stop the bleeding and he died Release of the prostatic fibrinolytic enzyme may have been initially responsible and vascular hypoxia and resultant increased capillary permeability were believed contributory Plasminemia was demonstrated in a third patient who had splenectomy Despite massive hemorrhage during operation and clotting failure the patient made a good recovery after administration of whole blood and serum albumin In the fourth plasminemia developed during shock associated with postpartum hemorrhage and adherent placenta Active fibrinolysis was present but there was no incoagulability of the blood to suggest entry of amniotic fluid into the circulation and plasma fibrinogen was normal Immediate therapy essentially obliterated proteolytic activity and controlled bleeding Plasminemia probably caused a hemorrhage tendency in the last patient treated for gunshot wounds It was difficult to assess the role of shock and liberation of tissue enzymes may also have contributed Whole blood and serum albumin controlled generalized bleeding

Abnormal proteolytic activity may be encountered under the following circumstances (1) activation of plasminogen by a general alarm reaction (2) through release into circulation of tissue activator substances (e g from the lung) (3) entry into circulation of proteolytic enzymes *other than plasmin* from sources such as prostate or pancreas (4) amniotic fluid embolism In any situation surgical or other

wise of abnormal bleeding without local cause plasminemia must be considered Excluding hemophilic entities due to reduction in some coagulation factor most cases of inordinate bleeding during or following operation are due to hyperheparinemia or plasminemia With plasminemia coagulation time may be normal with subsequent partial or complete lysis of the clot or there may be no coagulation Hyperheparinemia can be excluded if there is dissolution of the clot If blood is incoagulable addition of thrombin causes clotting with hyperheparinemia but not with plasminemia

Once the base line blood sample has been obtained therapy consisting of whole blood for supplementary antiplasmin and to supply substrate in the form of fibrinogen prothrombin and other coagulation factors low salt human serum albumin to oppose plasminemia directly by providing antiplasmin Toluidine blue an established antiheparin agent should be instituted immediately on empiric grounds When the presence of plasminemia is established toluidine blue is discontinued

The Heart *and* Blood Vessels *and* The Kidney

TINSLEY R HARRISON M D

PART IV

THE HEART AND BLOOD VESSELS AND THE KIDNEY

CONGENITAL HEART DISEASE

Diagnostic Roentgenology in Congenital Heart Disease is discussed by Martin H Wittenborg and Edward B D Neuhauser[1] (Boston) Roentgenograms fail to distinguish the normal heart from the majority of hearts with congenital lesions at or shortly after birth Also no simple roentgenographic cardiac measurements yet devised are practical in infancy and early childhood Physiologic variations in size during respiration exceed pathologic variations for any given stage of the respiratory cycle

There are no universal roentgenologic criteria of left and right ventricular enlargement The commonest stumbling block is recognition of right sided enlargement which ordinarily does not add appreciably to transverse heart diameter It is best demonstrated in oblique projections Right ventricular hypertrophy with moderate enlargement but unbalanced by a normal left ventricle results in the classic coeur en sabot shape however if balanced by a well developed or enlarged left ventricle the effect resembles that seen in acquired mitral insufficiency with stenosis Cardiac chamber enlargement means disease but disease may exist without enlargement In general if a ventricle is working against increased resistance or pressure myocardial hypertrophy with little change in heart size is common

A poor excursion of the cardiac border indicates pericardial fluid or myocardial weakness or both Increased amplitude of pulsation of the pulmonary artery and aorta together indicates an extracardiac shunt or high septal defect Actual thinning of a vessel wall may be reflected by an in

[1] Circulation 11 462-4 5 March 1955

crease in amplitude of pulsation even in presence of low pressure and diminished flow as in localized poststenotic dilatation of the pulmonary artery

Normal pulmonary vasculature seen in roentgenograms is almost entirely arterial Increase in vessel size or caliber best recognized in middle lung fields represents increase in content i e pulmonary hyperemia Intrapulmonary congestion (increased density of bronchial or interstitial supporting tissues) suggests passive engorgement Active expansile pulsation of vessels at fluoroscopy is evidence of active engorgement secondary to left to right shunt Diminished pulmonary vasculature is practically pathognomonic of diminished pulmonary blood flow most common in pulmonic stenosis

Expansile pulsation of pulmonary vessels an actual increase in transverse diameter of the vascular shadow during systole is to be distinguished from mere rhythmic movement secondary to respiratory activity or transmission of pulsation by proximity to the heart or great vessels Expansile pulsation distal to the secondary and tertiary divisions of the hilus almost invariably means increased pulmonary blood flow and is most commonly seen in atrial septal defects high or large ventricular septal defects and truncus communis and less commonly in patent ductus arteriosus It is lost in the older age group if pulmonary hypertension intervenes

In many patients with deficient pulmonary blood flow the vascular pattern is altered by collateral circulation through the bronchial arteries which are more tortuous lack linear radial distribution and fail to emanate from a central point in the hili This picture is common in tetralogy of Fallot and is sometimes seen with tricuspid atresia It has never been observed in uncomplicated pulmonic stenosis

Roentgenographic and fluoroscopic observations gain significance only by correlation with information gained by other methods Major division of cases usually is physiologic based on presence absence or late appearance of cyanosis Malformations of acyanotic type are subdivided into those presenting evidence of congenital stenosis (coarctation of aorta aortic and subaortic stenosis pulmonary stenosis) and those showing a defect between pulmonary and

systemic circulation permitting abnormal shunting of blood from left to right (interauricular or interventricular septal defects and extracardiac lesions such as patent ductus arteriosus and aortic pulmonic defect) If cardiac cyanosis is present a flow defect is assumed between pulmonary and systemic circulations in the opposite direction i e a right to left shunt This may be secondary to pulmonary hypertension associated with the simple lesions already listed to multiple defects (e g tetralogy of Fallot tricuspid atresia pulmonic stenosis with atrial septal defect or foramen ovale or Ebstein s deformity with atrial septal defect) or to major malformations resulting in an admixture of pulmonary venous and systemic arterial blood (e g truncus communis complete transposition single ventricle bilocular heart and other rare lesions) If cyanosis is inconstant or appeared later (4th to 6th year) it is assumed that a left to right shunt has reversed itself this usually is associated with pulmonary hypertension Once the hearts have shifted to the right they assume a uniform appearance and are indistinguishable from one another

History physical examination ECG film and fluoroscopic examinations if properly correlated should yield a working physiologic diagnosis in 85% of patients with congenital heart disease The exact nature of the lesion in half the remaining 15% may become clear after angiocardiography or catheter tudies or both

Venous Pulse in Atrial Septal Defect A Clinical Sign John Reinhold[2] (London) believes that a large *v* wave in atrial septal defect is useful in differentiating this condition from pulmonary stenosis

Inspection of the neck veins in children with atrial septal defect reveals a raised venous pressure and exaggeration of one of the waves of the venous pulse Simultaneous auscultation identifies thi large wave by its relation to the second heart sound as the *v* wave When pulmonary hypertension is present in these patients the *a* wave also becomes larger than normal Recordings of the venous pulse in 25 patients with atrial septal defect compared with 16 normal children confirmed these findings There is also exaggeration of normal systolic collapse in these patients which contributes to the prominence of the *v* wave

(2) Brit b M J 1 695 698 M 19 1955

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Total Pulmonary Venous Drainage through Persistent Left Superior Vena Cava William Whitaker[4] (Royal Hosp Sheffield) reports eight cases of an anomaly that may not be so rare as previously believed Behind the heart the right and left pulmonary veins join into a common pulmonary vein which runs into a persistent left superior vena cava passing in turn upward in front of the left pulmonary artery into the left innominate vein or directly into the right superior vena cava Thus the oxygenated pulmonary venous blood enters the right heart and mixes in the right atrium with systemic venous blood Blood then passes from this to both systemic and pulmonary circulations the former is supplied exclusively by blood which enters the small left atrium through an atrial septal defect Systemic blood flow and pressure are sometimes low and pulmonary blood flow and blood pressure are usually increased

Exertional dyspnea and recurrent pulmonary infections characterize the anomaly Physical development is retarded Cyanosis and finger clubbing were slight in the author s patients The dominant murmur if it occurred was basal and systolic—heard maximally over the pulmonary area There is auscultatory evidence of pulmonary hypertension and inspection often discloses a right ventricular type of impulse with prominence of the left chest ECG evidence of right ventricular dominance was present X ray studies reveal an ovoid upper mediastinal mass and enlarged heart with prominent pulsations in the pulmonary arteries and mediastinal mass The appearance is apparently diagnostic Angiocardiography may confirm the diagnosis Cardiac catheterization demonstrated the persistent left superior vena cava by passage of the catheter from the right median cubital vein through the innominate veins and via the left superior vena cava into a pulmonary vein The catheter was also passed through the atrial septal defect Blood samples from the right heart and femoral artery had virtually the same oxygen saturation There is no satisfactory surgical treatment but often the disability is minimal and patients frequently grow to adulthood

Drainage of Right Pulmonary Vein into Inferior Vena Cava *Report of Case with Radiologic Analysis of Principal* **Types of Anomalous Venous Return from Lung in 19**

(4) B t H rt J 16 177 288 Ap 1 1954

Cor Triatriatum Rare Malformation of Heart Probably Amenable to Surgery Report of a Case with Review of Literature Asger Pedersen and F Therkelsen[3] (Univ of Copenhagen) describe two general types hearts with abnormal cords bands or reticula in the left atrium (probably always harmless) and actual septum formation across the lumen of the left atrium subdividing it into two distinct compartments The upper or posterior chamber usually larger and often funnel shaped receives all the pulmonary venous drainage the lower or anterior chamber connects with the opening of the auricular appendage The septum may be a thin membrane or several millimeters thick usually one or more perforations exist In 23 cases in the literature of real cor triatriatum the diaphragm in 2 was complete the only pathway of arterial blood being through defects in the atrial septum and in 1 through displaced pulmonary veins Most patients died in the first years of life although a few with fairly large septal openings reached adulthood The mitral valve was nearly always normal Rather often symptoms were slight or lacking until death from rapidly developing congestive heart failure No attacks of acute pulmonary edema have been reported although the predominant symptom is dyspnea usually with cyanosis and syncope

Stethoscopic findings were generally inconclusive X ray examination reported for eight cases usually showed diffuse cardiac enlargement with relative left atrial enlargement suggested only once ECG s recorded in only three cases showed right axis deviation and signs of right ventricular hypertrophy but no definite abnormality of P waves Cardiac catheterization in the authors patient showed excessive pulmonary hypertension with moderate increase during exercise a high pulmonary capillary pressure which reflected no atrial pressure curve normal right atrial pressure curve no evidence of a left to right shunt normal oxygen saturation and no decrease in cardiac output Digital exploration and identification of the anomalous septum during thoracotomy was not performed but in retrospect the authors consider that a diagnosis could in this way have been made Wide splitting or finger fracture of the anomalous diaphragm may offer surgical relief in these cases

(3) Am. Heart J 47 676-691 May 1954

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(4) B t H rt J 16 177 88 Ap 1 1954

additional cases is presented by Victor A McKusick and Robert N Cooley[5] (Johns Hopkins Univ)

Routine chest x ray in a Negro girl, 17 during her first preg nancy showed a peculiar cardiac configuration with prominent right border interpreted as cardiac displacement No abnormal lung shadow was noted. Five years later still asymptomatic she was referred because a tuberculosis survey had revealed the same un usual finding along with a sickle shaped or inverted comma shaped shadow in the right lung field Angiograms revealed dilatation of right atrium ventricle and main pulmonary artery The sickle shaped shadow in the right lung filled at the same time as veins of the left lung and showed clear communication with the inferior vena cava just below its entry into the right atrium It could not be established whether this anomalous vein perforated the diaphragm At age 25 patient had passed through six normal pregnancies with out event She was then moderately obese and had easy fatigability mild dyspnea with exertion and cardiac consciousness Attempts to catheterize the anomalous right pulmonary vein and both pulmo nary arteries were unsuccessful

The fundamental hemodynamic abnormality in transposi tion of pulmonary veins is shunting back to the right side of the circulation of blood normally destined for the left atrium and systemic circulation Roentgenologically as in interatrial septal defect increased vascularization of lung fields and hilar dance are likely to occur The right atrium is dilated as a rule and the right ventricle dilated and hyper trophied The superior vena cava may also be dilated There may be slight outpouching of the superior vena cava where the anomalous pulmonary vein enters or changes in the upper mediastinum from dilatation of the normal right su perior vena cava or of a persistent left superior vena cava that receives blood from the lungs Angiocardiograms gener ally reveal dilatation of the right atrium right ventricle and pulmonary artery On first circulation there is likely to be considerable dilution of contrast medium where pulmonary blood joins the systemic venous return the superior vena cava may enlarge abruptly at this point Recirculation through the right side of the heart can usually be shown Anomalous veins are often outlined satisfactorily and their drainage demonstrated

In 19 cases reviewed several varieties of anomalous drainage were noted In four cases there appeared to be par tial return of pulmonary veins to the superior vena cava Partial drainage directly into the right atrium by veins

(5) New England J Med 252 291 301 Feb 24 1955

of the right lung was seen in one case Partial drainage of left pulmonary veins to the right atrium via a persistent superior vena cava on the left and the coronary sinus was found in two Three cases showed total drainage of pulmonary veins into the right atrium and one to the superior vena cava on the right via the azygos vein The figure-of eight syndrome in which all pulmonary veins return to the right side of the heart was seen in eight cases

This malformation could probably have been suspected from ordinary chest x rays in 11 cases In five others angiocardiography suggested or established diagnosis

Anomalous Pulmonary Venous Drainage into Left Vertical Vein Bertram Levin and Craig W Borden[6] (Univ of Minnesota) state that pulmonary veins have been found to drain anomalously into the superior vena cava coronary sinus portal vein right atrium innominate veins sinus venosus azygos vein and even the thoracic duct All or part of the pulmonary venous blood may be diverted from the left atrium into systemic veins

One of the more frequent aberrations of pulmonary venous return is emptying of the pulmonary veins into the left vertical vein The latter is a wide vertical vascular structure to the left of and adjacent to the base of the heart linking the pulmonary veins with the left innominate vein The x ray features of this anomaly are characteristic and resemble a figure 8 The upper loop is formed by the dilated superior vena cava and the left vertical vein the lower by the heart The superior mediastinum is widened The right ventricle is greatly enlarged The hilar and peripheral pulmonary arteries are dilated because of the increased pulmonary blood flow Angiography may show not only the left vertical vein but also a large shunt into the innominate vein and superior vena cava

When anomalous pulmonary venous return is only partial and there are no major intracardiac abnormalities few symptoms beyond mild exertional dyspnea are produced The anomalous vessel may not be suspected and be discovered at thoracotomy If however an appreciable volume of blood is shunted through an anomalous pulmonary vein from left to right a natural history similar to that of interatrial septal defect can be anticipated The shunt in

(6) ... 317 3 4 September 1954

additional cases is presented by Victor A McKusick and Robert N Cooley[5] (Johns Hopkins Univ)

Routine chest x ray in a Negro girl 17 during her first pregnancy showed a peculiar cardiac configuration with prominent right border interpreted as cardiac displacement No abnormal lung shadow was noted Five years later still asymptomatic she was referred because a tuberculosis survey had revealed the same unusual finding along with a sickle shaped or inverted comma shaped shadow in the right lung field Angiograms revealed dilatation of right atrium ventricle and main pulmonary artery The sickle-shaped shadow in the right lung filled at the same time as veins of the left lung and showed clear communication with the inferior vena cava just below its entry into the right atrium It could not be established whether this anomalous vein perforated the diaphragm At age 25 patient had passed through six normal pregnancies without event She was then moderately obese and had easy fatigability, mild dyspnea with exertion and cardiac consciousness Attempts to catheterize the anomalous right pulmonary vein and both pulmonary arteries were unsuccessful

The fundamental hemodynamic abnormality in transposition of pulmonary veins is shunting back to the right side of the circulation of blood normally destined for the left atrium and systemic circulation Roentgenologically as in interatrial septal defect increased vascularization of lung fields and hilar dance are likely to occur The right atrium is dilated as a rule and the right ventricle dilated and hypertrophied The superior vena cava may also be dilated There may be slight outpouching of the superior vena cava where the anomalous pulmonary vein enters or changes in the upper mediastinum from dilatation of the normal right superior vena cava or of a persistent left superior vena cava that receives blood from the lungs Angiocardiograms generally reveal dilatation of the right atrium right ventricle and pulmonary artery On first circulation there is likely to be considerable dilution of contrast medium where pulmonary blood joins the systemic venous return the superior vena cava may enlarge abruptly at this point Recirculation through the right side of the heart can usually be shown Anomalous veins are often outlined satisfactorily and their drainage demonstrated

In 19 cases reviewed several varieties of anomalous drainage were noted In four cases there appeared to be partial return of pulmonary veins to the superior vena cava Partial drainage directly into the right atrium by veins

(5) New England J Med 252 291 301 Feb 24 1955

of the right lung was seen in one case Partial drainage of left pulmonary veins to the right atrium via a persistent superior vena cava on the left and the coronary sinus was found in two Three cases showed total drainage of pulmonary veins into the right atrium and one to the superior vena cava on the right via the azygos vein The figure of eight syndrome in which all pulmonary veins return to the right side of the heart was seen in eight cases

This malformation could probably have been suspected from ordinary chest x rays in 11 cases In five others angiocardiography suggested or established diagnosis

Anomalous Pulmonary Venous Drainage into Left Vertical Vein Bertram Levin and Craig W Borden[6] (Univ of Minnesota) state that pulmonary veins have been found to drain anomalously into the superior vena cava coronary sinus portal vein right atrium innominate veins sinus venosus azygos vein and even the thoracic duct All or part of the pulmonary venous blood may be diverted from the left atrium into systemic veins

One of the more frequent aberrations of pulmonary venous return is emptying of the pulmonary veins into the left vertical vein The latter is a wide vertical vascular structure to the left of and adjacent to the base of the heart linking the pulmonary veins with the left innominate vein The x ray features of this anomaly are characteristic and resemble a figure 8 The upper loop is formed by the dilated superior vena cava and the left vertical vein the lower by the heart The superior mediastinum is widened The right ventricle is greatly enlarged The hilar and peripheral pulmonary arteries are dilated because of the increased pulmonary blood flow Angiography may show not only the left vertical vein but also a large shunt into the innominate vein and superior vena cava

When anomalous pulmonary venous return is only partial and there are no major intracardiac abnormalities few symptoms beyond mild exertional dyspnea are produced The anomalous vessel may not be suspected and be discovered at thoracotomy If however an appreciable volume of blood is shunted through an anomalous pulmonary vein from left to right a natural history similar to that of interatrial septal defect can be anticipated The shunt in

(6) Radiology 63 317 324 September 1954

creases the work of the right ventricle Pulmonary hyper tension and right heart failure may develop

With complete anomalous pulmonary venous drainage dyspnea and cyanosis are invariably present Although the latter is usually mild its presence suggests the diagnosis of congenital heart disease Paroxysms of supraventricular tachycardia and palpitation may occur Polycythemia is absent or mild although arterial oxygen saturation is slightly but definitely lowered The ECG shows severe right axis deviation and right ventricular strain These clinical findings are not specific but in conjunction with the typical x ray picture they permit an accurate diagnosis

Definitive diagnosis requires cardiac catheterization to obtain blood with a high oxygen saturation from the left vertical vein or at its junction with the innominate vein

Congenital Cardiovascular Anomalies Induced by Pteroylglutamic Acid Deficiency during Gestation in the Rat Published studies have shown that when normal female rats are given a diet deficient in pteroylglutamic (folic) acid from the 10th or 11th day of pregnancy on 95 100% of the offspring exhibit multiple congenital anomalies Catherine D C Baird Marjorie M Nelson Ian W Monie *and Herbert M Evans*[7] *(Univ of California)* studied the nature and incidence of cardiovascular anomalies in fetal rats of mothers given a diet deficient in folic acid for varying periods during gestation

Congenital cardiovascular anomalies were produced in 28 57% of the offspring of pregnant rats given the folic acid deficient diet for only two or three days starting on the 7th 9th or 10th day of gestation Both cardiac and vascular anomalies were observed in all groups although the group receiving the folic acid deficient diet during days 7 9 had a higher incidence of cardiac than of vascular anomalies whereas vascular anomalies were more prevalent when the diet was started on day 9 or 10 When the diet was started only one day later no macroscopic defects of the cardiovascular system were observed

The following cardiovascular anomalies were observed interventricular septal defects persistent truncus arteriosus double or right aortic arch absence of *the ductus* arteriosus aberrant origins of the subclavian arteries and

(7) Circulation Res. 2 544-554 November 1954

additional variations of the arterial pattern derived from the embryonic arch system Wilson *et al* observed similar anomalies in chronic maternal vitamin A deficiency

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VALVULAR DISEASE AND MURMURS

Cortisone Therapy of Initial Attacks of Rheumatic Carditis I Clinical Data Lawrence Greenman F A Weigand F M Mateer and F S Danowski[8] (Univ of Pittsburgh) report their experience in 53 children treated with large doses of cortisone in their initial attack of clinically unequivocal rheumatic carditis The therapeutic regimen included bed rest Most children were given 100 mg cortisone orally every eight hours for six weeks then tapering doses until therapy was stopped after two more weeks If the disease was still active at the end of this interval the patient was re treated During therapy diets were limited in sodium to 2 5 10 mEq /day and contained 150 mEq potassium and adequate protein and calories with supplementary iron and vitamins Penicillin 400 000 or 800 000 units intramuscularly or 500 000 units orally was given twice a day for the first week then 100 000 units of buffered penicillin orally three times a day between meals Digitalis and mercurial diuretics were given it congestive heart failure was present Complications during treatment such as hyperadrenalism mental changes and abdominal distention did not contraindicate continued therapy except in one patient with toxic psychosis

There were significant differences in results when outcome was evaluated according to duration of illness before treatment Of the 14 patients sick less than two weeks 12 (86%) had no residual cardiac abnormalities at the end of therapy one was left with a murmur and one had both cardiac enlargement and murmurs No one showed evidence of rheumatic fever at the end of therapy The group treated between two and six weeks resembled those treated within the first two weeks Of the patients sick more than six weeks only 7% were normal at end of therapy In no patient was cardiac abnormality greater than on admission

(8) A M A Am J D Child 89 426 441 April 1955

Cardiac enlargement had an adverse influence on results of treatment although a third of all patients with enlargement had normal hearts after treatment half of those treated within the first six weeks showed this improvement When no enlargement was present before therapy 7-90% of the patients had completely normal hearts at final evaluation

Follow up studies 3 39 months after therapy showed that 53% of the entire group had no demonstrable cardiac abnormality by physical examination before and after exercise teleroentgenograms with barium swallow or fluoroscopy

Although the mechanism of cortisone action is not clear it is suggested that this steroid in sufficiently large amounts suppresses the inflammatory reaction of rheumatic fever The exact duration of treatment is not known, and in some patients years of treatment may be necessary It may be advisable to administer cortisone to all children with rheumatic fever as soon as diagnosis is established Preferably it should be given before clinically evident carditis is recognized in order to prevent residual damage

New Method of Determining Degree or Absence of Mitral Obstruction Analysis of Diastolic Part of Indirect Left Atrial Pressure Tracings S G Owen and Paul Wood[9] correlated the form of the indirect left atrial pressure record in mitral valve disease with the presence and relative importance of stenosis and incompetence in 54 patients

METHOD—*Indirect left atrial tracings were obtained by wedging a cardiac catheter during inspiration in a distal branch of the pulmonary artery and recording pressures by a Sanborn electromanometer using hydraulic damping and a Polyviso direct writing recorder Measurements of the v ascent and y descent were made from the tracings the term y representing the decline of atrioventricular diastolic flow and the v wave the positive deflection of the left atrial pulse associated with passive atrial filling against a closed mitral valve For measurement vertical intervals were interpolated by eye to 0 5 mm and time intervals to 0.25 mm (0 01 second) The average rate of y descent in mm Hg/second was obtained by this formula*

$$R_y = \frac{(p - p_1)\ \text{mm} \times \text{calibration factor}}{(t - t)\ \text{second}}$$

The point p_1 is the first point on the v wave free from sound artefact at which a pressure fall is perceptible and p is either the

(9) Brit. Heart J 17 41 55 January 1955

point at which the descent first reaches its subsequent isotonic level or if it continues throughout diastole until interrupted by atrial contraction or mitral valve closure the last point on the slope un obscured by these events t and t are corresponding point on the time scale The brief terminal dip below the isotonic sometimes displayed by the y descent was ignored in calculating R p being taken immediately before the dip The ratio between R_y and v was derived by inserting the height of v in millimeters above the zero reference point (p) into the denominator and removing the calibra tion factor from the numerator

$$R_y/\text{v} = \frac{(p \; - p\;)\ \text{mm}}{p\ \text{mm} \times (t \; - t\;)\ \text{second}}$$

In pure or dominant stenosis the time for inscription of y descent is significantly prolonged The most stable expres sion of this proved to be the quotient of the calculated rate of fall divided by the height of the preceding v wave in mm Hg above the sternal angle This value remains rela tively independent of individual fluctuations in mean pres sure and diastolic length When left atrial pressure is raised the ratio may vary as the pressure flow relationship across the mitral valve With one exception the ratio was less than 1 5 in examples of pure stenosis and invariably exceeded this in moderate incompetence When incompetence was the only significant lesion the ratio was greater than 2 2 A value greater than 1 6 is unlikely to occur if stenosis is pure or associated with only trivial incompetence It may be concluded that the pattern of the left atrial pressure pulse during diastole is determined by the presence and de gree of mitral stenosis and the R_y/v ratio seems a useful expression of this pattern

[The details of the formulas given here are not important but the principle is Obviously blood will move more readily through a widely open than through a narrow orifice The technic described therefore offers i portant information concerning this po nt In the editor s expe r ence the stethoscope has previously offered the most reliable informa tion as to the presence or absence of mitral stenosis and insufficiency However the stethoscope has not been too reliable as a guide to the relative degree of each Any procedure which g ves accurate information concerning th s point should be of d rect practical value in selecting patie ts for mitral valvulotomy —Ed]

Appreciation of Mitral Stenosis —*I Clinical features* — Paul Wood[1] analyzed 300 cases of mitral valvular disease 150 of which were unsuitable for operation and synthe

(1) B t M J 1 1052 1063 M y 8 1954

Cardiac enlargement had an adverse influence on results of treatment although a third of all patients with enlargement had normal hearts after treatment half of those treated within the first six weeks showed this improvement When no enlargement was present before therapy 75 90% of the patients had completely normal hearts at final evaluation

Follow up studies 3 39 months after therapy showed that 53% of the entire group had no demonstrable cardiac abnormality by physical examination before and after exercise teleroentgenograms with barium swallow or fluoroscopy

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(9) Brit. Heart J 17 41 55 Jan ary 1955

evaluation is the most reliable guide to the presence and degree of mitral insufficiency in the preoperative study of a patient with rheumatic heart disease Not only the systolic mumur but the position and nature of the apex impulse and the quality of the mitral first sound are significant The authors discount the value of the presence or absence of the opening snap of the mitral valve In their experience systolic expansion of the left atrium as seen by x ray has not been a reliable guide to the functional condition of the mitral valve Other radiologic observations are valuable corollary contributions in the evaluation of cardiac status Electrocardiographic findings have proved inferior to clinical data as a guide to the presence and degree of mitral incompetence

In 53 patients who had had operations performed Aschoff nodes were found in about a third In two patients active rheumatism developed postoperatively At thoracotomy evidence of recent or old pleural or pulmonary disease was found in a high proportion of cases Finger fracture was preferred to the use of the valvotome Postoperatively pulmonary emboli were fairly common and the source was thought to be the right auricle Five deaths occurred in the series Of the survivors 33 were followed for 6 months and 18 for as long as a year About 70% derived significant benefit

Medical Aspects of Patients Undergoing Surgery for Mitral Stenosis are described by Lewis Dexter Lawson McDonald Murray Rabinowitz George A Saxton Jr and Florence W Haynes[4] (Harvard Med School) using experience gained in selection and management of 600 patients

The patients were placed in four categories Stage 1 no increased pulmonary vascular resistance and subcritical narrowing of the mitral valve (orifice greater than 1.2 sq cm) Symptoms are few and activities are voluntarily limited by exercise tolerance Stage 2 little or no increase in pulmonary vascular resistance and critical narrowing of the mitral valve (orifice less than 1.2 sq cm) Severe pulmonary distress accompanies mild exertion Resting pulmonary capillary pressure is near the threshold of pulmonary edema ECG and x ray evidence of right ventricular hy

(4) C culat on 9 758 770 M y 1954

sized clinical and laboratory features of patients with the various valvular involvements typical of rheumatic heart disease

Peripheral cyanosis of the face and hands was common and has been attributed to vasoconstriction secondary to low cardiac output A presystolic murmur was heard in virtually every case unless there was considerable mitral insufficiency The presence of such a murmur constitutes good evidence against regurgitation The first heart sound was loud in the presence of mitral stenosis without significant insufficiency but gave little indication of the degree of stenosis No case of significant mitral insufficiency without a moderate or loud systolic murmur was encountered Observations indicated that presence of the opening snap of the mitral valve is excellent evidence against serious mitral insufficiency the existence of the third heart sound favors at least moderate mitral incompetence and is sufficient reason not to recommend valvotomy Evaluation of the pulmonary second sound is helpful but not infallible in estimating pulmonary hypertension

II Investigation and results—From ECG tracings Wood[2] found that the P mitral if prominent is a good sign of mitral stenosis The degree of right ventricular preponderance is closely related to pulmonary vascular resistance Any degree in mitral stenosis warrants valvotomy Existence of left ventricular preponderance however is excellent evidence of mitral incompetence in the absence of aortic valve disease

Pulmonary vascular resistance is a most important physiologic factor Its extent largely determines the course and pattern of the disease The size of the mitral orifice thus is the fundamental factor which determines the severity of the disease and pulmonary vasoconstriction is the most important physiologic reaction which modifies its course and behavior

Results of surgery were excellent or good in 70% of cases Mortality rate was 6% Systemic embolism was the principal major surgical complication

Some Aspects of Mitral Disease in Relation to Surgical Treatment are discussed by D M Douglas and Ian G W Hill[3] (Univ of St Andrews) who believe that clinical

(2) Brit M J 1 1113 1124 May 15 1954
(3) Ed burgh M J 61 133 154 May 1954

fibrillation Postoperative dilution hyponatremia is correctable by restriction of salt and water intake Anticoagulants are not used routinely All patients should have permanent prophylactic treatment with antibiotics as the operation does not confer immunity to recurrent rheumatic activity

Assessment of Mitral Stenosis by Phonocardiography may constitute a valuable addition to the many and sometimes misleading methods for diagnosis of the severity of the valve lesion Bertrand Wells[5] (St Bartholomew s Hosp London) demonstrates that the phonocardiogram in mitral stenosis usually shows two abnormal features an increase in time interval between onset of the QRS complex of the ECG (taken simultaneously) and onset of maximal vibrations of the 1st heart sound (Q 1 interval) and the vibrations caused by the opening snap which follows the 2d sound The interval between the beginning of the 2d sound and beginning of the opening snap is designated 2 O S These intervals vary with the length of the preceding cardiac cycle after a short R R interval Q 1 is long and 2 O S short and as the R R interval lengthens Q 1 becomes shorter while 2 O S becomes longer These variations are determined by the pressure gradient across the mitral orifice With a high pressure gradient after a short diastolic interval the left ventricle takes longer to reach atrial pressure and the 1st sound is delayed As atrial pressure remains high throughout systole the opening snap occurs early Although these relationships are not rigorous and other factors undoubtedly are influential they are at least indicative

Pre and postoperative phonocardiographic studies were performed on 30 patients who had mitral valvotomy Of these 27 had an opening snap shown on the phonocardiogram the other 3 were eliminated from the study Graphs of Q 1 2 O S and R R demonstrated essentially linear correlation and the Q 1 and 2 O S intervals were read off without extrapolation for a cycle length of 0 8 seconds (termed corrected intervals) These were compared with the product of the length and breadth of the mitral valve orifice as estimated by the surgeon There was a close relationship between corrected Q 1 minus corrected 2 O S and the size of the mitral orifice For figures between +5 and −1

(5) Brit Heart J 16 261 266 J ly 1954

pertrophy may or may not be present Stage 3 moderate increase in pulmonary vascular resistance (6 10 times normal) and further narrowing of the mitral valve (1 sq cm or less) Fatigue from diminished cardiac output causes curtailment of activity and dyspnea may be masked by fatigue There are ECG evidence of right ventricular hypertrophy and radiologic evidence of enlargement of the left auricle right ventricle and pulmonary artery with generalized cardiac enlargement Stage 4 severe degree of pulmonary vascular resistance and severe narrowing of the mitral valve (0 8 sq cm or less) These terminal patients have low cardiac output borderline pulmonary edema at all times and severe respiratory symptoms which are more apparent than the fatigue

Operation is indicated in stages 2 3 or 4 and is recommended for arterial embolism whether or not cardiac incapacity is present Patients in stage 1 are not operated on Advancing age is not itself a contraindication and severely ill (stage 4) patients are not denied operation which even in this group has a 77% salvage rate Aortic stenosis is a contraindication if it is significant This can be estimated by prolongation of the systolic upstroke (greater than the reciprocal of the square root of the pulse rate) in brachial artery tracings Aortic regurgitation is probably insignificant if the diastolic pressure is 50 mm Hg or more If mitral regurgitation is significant with ECG evidence of left or bilateral ventricular hypertrophy but not of right ventricular hypertrophy alone and with dilatation of the left auricle and possibly of the left ventricle on x ray surgery is contraindicated Tricuspid regurgitation is no bar to surgery but if tricuspid stenosis is present the surgeon should be prepared to operate on that valve immediately after the mitral Rheumatic activity is not considered a contraindication to surgery if the valve orifice is severely stenosed Subacute bacterial endocarditis pregnancy and recent pulmonary infarction delay surgery

All patients are digitalized and given a low salt diet preoperatively During surgery calcium chloride and epinephrine may be used to improve poor myocardial contractility neostigmine for auricular arrhythmias and pronestyl® for ventricular irritability Quinidine is given patients with normal sinus rhythm postoperatively to pr iricular

done while she was in right and left sided congestive failure demonstrated severe pulmonary hypertension with high right ventricular diastolic pressure low cardiac output and large blood volume After digitalization mercurials and bed rest striking reduction in right heart pressures occurred with rise in cardiac output After further treatment this patient might present the same hemodynamic picture at rest as the others in group II

Without proved moderate to severe pulmonary hypertension at rest there is probably little or no important degree of block at the mitral valve Patients with mitral stenosis and little or no hypertension must be carefully evaluated They should not have commissurotomy since they may have predominantly myocardial insufficiency or no circulatory dysfunction

Clinical Determination of Mitral Insufficiency When Associated with Mitral Stenosis *A review by* O Henry Janton Guenther Heidorn Louis A Soloff Thomas J E O Neill and Robert P Glover[7] (Philadelphia) of 200 cases of pure mitral stenosis and 47 of stenosis with insufficiency in which mitral commissurotomy had been done revealed that careful evaluation of history auscultation findings electrocardiograms and fluoroscopy observations permits a correct diagnosis of associated insufficiency in most instances Re ults with cardiac catheterization auricular esophagograms electrokymography phonocardiograms ballistocardiograms and perbronchial direct measurement of left atrial pressure are incompletely evaluated as yet The regurgitant jet was graded (0-4) at operation and patients with a jet of 2 or more were considered to have mitral insufficiency

The patient with pure mitral insufficiency remains relatively free from symptoms for a longer period than the patient with pure mitral stenosis When disability occurs fatigue rather than dyspnea is first noticed In the presence of both lesions the incapacitation produced by mitral stenosis usually dominates the picture Systemic arterial emboli appear much less frequently when the mitral valve is both stenotic and insufficient The characteristic murmur of pure mitral insufficiency is usually rough grade 3 or 4 and holosystolic It is generally heard best at the mitral area be

(7) C lat on 10 207 212 A gu t, 1954

the orifice was always under 1 × 1 cm whereas for figures between −1½ and −4 all but one of the mitral orifices were larger Comparison also showed that all but one of the patients with improvement in the phonocardiogram postoperatively had an original mitral orifice smaller than 1 × 1 cm, all patients with no improvement had larger orifices These preliminary studies may provide a valuable preoperative aid

Mechanical and Myocardial Factors in Rheumatic Heart Disease with Mitral Stenosis were studied by cardiac catheterization in 16 patients by Rejane M Harvey M Irene Ferrer Philip Samet Richard A Bader Mortimer E Bader Andre Cournand and Dickinson W Richards[6] (Columbia Univ) Analysis of hemodynamic data permitted separation of eight patients with predominantly mechanical mitral block (group I) from eight (group II) in whom myocardial insufficiency was dominant In any rheumatic subject these dysfunctions may coexist equally or in varying proportions All 16 subjects had cardiovascular symptoms 12 had had pulmonary or peripheral congestion at some time Group I had almost constant and often progressive disability group II though completely incapacitated occasionally, had relatively asymptomatic periods when they could resume work

All eight patients with mitral stenosis had progressive cardiac disability with pulmonary hypertension and a low or normal cardiac output with diminished blood flow during leg exercise Following commissurotomy and widening of the mitral orifice to 2 finger widths pulmonary hypertension decreased both at rest and during exercise in every patient but in none was there decrease in cardiac output or significant difference in heart rate In only one was pulmonary artery pressure restored to normal at rest and during exercise

In group II hemodynamic findings at rest were uniformly near normal Five had a rise of pulmonary hypertension during exercise two had resting pressures which did not increase significantly on effort One from each subgroup had mitral surgery with no improvement The eighth patient in group II represented a more advanced phase of predominantly myocardial insufficiency Her first study

(6) Circulation 11 531 551 April 1955

mur in relative mitral stenosis is often recorded over a wide area (all precordium in 30% spreading to the base in some and over a wide area beyond the apex in the others It al ways starts more than 0 15 second after the second sound A third sound is nearly always present (30 of 34 cases) in contrast to its rare occurrence in organic stenosis

Negative qualities include no opening snap of the mitral valve whereas this snap is frequent in organic mitral stenosis Also the main vibration of the first sound in rela tive stenosis has a normal relation to the beginning of QRS of the ECG (0 06-0 07) in organic mitral stenosis there is constant delay which may increase with severe arrhyth mia due to atrial fibrillation

The murmur of these cases seems to be due to dispropor tion between normal mitral ostium and large left ventricle causing eddies within the ventricle The large area of re cording can be explained by the large area of contact with the precordium of the left ventricle (coronary and hyper tensive cases) or of both ventricles (acute carditis)

Calcification of Mitral Valve Annulus and Its Relation to Functional Valvular Disturbance M A Simon and S F Liu[9] (Jewish Gen l Hosp Montreal) in a review of 590 unselected autopsy protocols found calcification of the mi tral valve annulus in 59 hearts The patients included 36 women and 23 men (average age 69) Average weight of the hearts with lesions was 454 Gm This increase in heart weight was due to hypertrophy caused by a variety of path *ologic cardiac conditions the most frequent being coro* nary arteriosclerosis and hypertension of variable degrees In 27% of the hearts variable degrees of aortic valve calci fication with variable degrees of stenosis were noted In only three cases of mitral annulus calcification was a diagnosis of rheumatic heart disease made pathologically

In 14 of the 59 hearts there was some degree of dilatation or hypertrophy of the left auricle or both Clinical data available in 11 of these cases showed that 7 patients had had an apical mitral systolic murmur only 1 had had evidence of rheumatic heart disease In three of the seven the mitral apical murmur had been either loud or musical Associated calcification of the aortic valve leaflets was present in 6 of the 11 cases and in 4 in which mitral apical systolic mur

(9) Am Heart J 48 497 505 Oct ber 1954

ginning with the first sound and frequently obscuring it It extends to and includes the aortic second sound Thirty per cent of the patients with pure mitral stenosis had a mitral systolic murmur in none was it grade 4 although six had a grade 3 murmur

An ECG pattern of left ventricular hypertrophy is seldom seen in patients with both stenosis and insufficiency nor is absence of a right ventricular hypertrophy pattern in the presence of clinically evident mitral stenosis suggestive of associated mitral insufficiency The only value of the ECG in differentiation of the predominance of mitral stenosis over mitral insufficiency is in disclosure of the left ventricular hypertrophy pattern when insufficiency is predominant In such cases the authors have not found commissurotomy beneficial No single procedure will accurately gauge the predominance of mitral insufficiency over mitral stenosis

Apical Diastolic Murmurs Simulating Mitral Stenosis II Graphic Differentiation Aldo A Luisada Olga M Haring and Aro B Zilli[8] (Chicago Med School) studied the graphic characteristics of apical murmurs in 34 patients Nine had congenital heart disease 16 acute rheumatic fever 6 coronary heart disease 4 syphilitic heart disease and 1 severe anemia Some had more than one condition

Every patient had a low pitched diastolic rumble presystolic murmur or both The functional nature of the murmur was proved by autopsy on 11 patients by disappearance following surgery (not on the mitral valve) in 2 and by appearance of the murmur during observation and disappearance after improvement in 21

For each case a complete clinical x ray and ECG study was made The phonocardiogram was recorded over apex midprecordium pulmonic aortic and tricuspid areas and tracings recorded by a Sanborn stethocardiette or twin beam fir t with a stethoscopic then with a logarithmic device

Certain positive data were helpful in recognizing the functional murmur The murmur is frequently loud like the first sound or louder in 30% of the cases and from half to two thirds of the first sound in 44% The lower amplitude is more often found with presystolic murmurs The mur

(8) Ann I t Med 42 644-653 M rch 1955

volvement Thus patients with this lesion usually have widespread rheumatic valvulitis and are poor surgical prospects However in certain cases the lesion is amenable to surgical correction The authors three patients had a history of right upper quadrant pain and ascites and awareness of pulsations or distention of the neck veins These findings early in the course suggest primary tricuspid involvement Two patients had stasis cyanosis of the facies although arterial oxygen saturation was normal The diastolic murmur of tricupsid stenosis is higher pitched and rougher than that of mitral stenosis In tricuspid insufficiency the murmur resembles that of mitral insufficiency but is located along the lower left sternal border A presystolic venous pulse wave proved to be an unreliable sign of surgical tricuspid stenosis Considerable hepatic enlargement was present in all patients but no intrinsic liver pulsations were detectable Fluoroscopy demonstrated prominence of the superior vena cava and right atrial enlargement

Analysis of the resting atrial pressure pattern obtained by catheterization showed a dominant a wave in two patients At operation they were found to have dominant insufficiency of the tricuspid valve although this has been said to be a diagnostic sign of tricuspid stenosis These patients also had mitral stenosis and mild tricuspid stenosis After exercise a high regurgitation wave with an approach to a ventricularization pattern was recorded Thus the effect of exercise on right atrial pressure is important in determining the significance of tricuspid insufficiency In the third patient who was found to have a tight tricuspid stenosis there was a high pressure gradient between the right atrium and right ventricle in early diastole The right ventricular pressure dropped to low levels during early diastole while the right atrial pressure remained elevated Reduction in the gradient followed operative enlargement of the tricuspid valve orifice This increase in the early diastolic gradient is perhaps the most dependable hemodynamic characteristic of surgical tricuspid stenosis

Clinical Features of Aortic Stenosis Avard M Mitchell Charles H Sackett Warren J Hunzicker and Samuel A Levine[2] (Peter Bent Brigham Hosp) reviewed the records

(2) Am. H rt J 48 684 720 N mbe 1954

murs were heard but in only 1 of the 4 was an aortic murmur recorded In two patients who had had murmurs over the aortic areas there was no calcification of the aortic valve One patient with calcification of the aortic valve had no mitral apical systolic murmur Heart block was found twice A clinical diagnosis of mitral regurgitation had been made in two cases and presystolic (diastolic) murmurs were recorded in three

Of 13 cases of marked mitral annulus calcification without evidence of left auricular hypertrophy or dilatation a mitral apical systolic murmur had been heard in 8 Thus mitral apical systolic mumurs occur with the same frequency in mitral annulus calcification without hypertrophy or dilatation of the left auricle as in those with left auricular enlargement In six of the eight cases the apical systolic murmur was described as loud or rough A questionable presystolic murmur was heard in two cases and a clinical diagnosis of mitral regurgitation was made in three

Thus apical systolic murmurs referable to the mitral valve were heard in 15 of 24 cases of calcification of the mitral valve annulus and in 9 murmurs were of special quality (loud rough or musical) A clinical diagnosis of mitral regurgitation was made in 5 of the 15 cases

It is suggested that extensive calcification of the mitral valve annulus interferes with the rhythmic muscular contraction of the mitral ring by forming a rigid noncompressible segment of that ring Thus the gap to be bridged may not be sufficiently reduced to permit the overlapping closure by the mitral leaflets The concept of interference with contraction of the valve ring with the observation that 60% of apical systolic murmurs in the proved cases of mitral annulus calcification have special qualities is considered presumptive evidence that extensive mitral annulus calcification (without rheumatic involvement of the leaflets) may produce relative or frank mitral regurgitation

Tricuspid Stenosis Clinical and Physiologic Evaluation is presented by Malcolm C McCord Henry Swan and S Gilbert Blount Jr[1] (Univ of Colorado) Autopsy has disclosed tricuspid stenosis in 10 15% of patients with valvular rheumatic heart disease It is almost always accompanied by mitral valve lesions and frequently by aortic valve in

(1) Am H rt J 48 405-415 S pt mbe 1954

pertension Subacute bacterial endocarditis occurred in 10% of the series The most valuable x ray finding was a calcified aortic valve

Venous Hum History Pathogenesis Incidence Recognition and Significance were studied by David Buttross[3] (Louisiana State Univ) This murmur is sometimes confused with others and a review of the literature leaves doubt as to its actual incidence particularly in adults and its significance Laennec apparently the first to note this sign erroneously thought it originated in the arteries Potain in 1867 first described the hum accurately noting that it is continuous and affected by respiration position and pressure

The exact mechanism of venous hum is not known Its usual site appears to be at the entrance of the internal jugular and subclavian veins into the innominate where turbulence of flow under certain circumstances is sufficient to produce a sound At these sites the blood stream caliber increases rather suddenly and velocity of flow is high It appears that essential conditions for production of the hum are present in everyone and that its occurrence depends on other factors the most important being velocity of flow viscosity of blood variations in architecture of veins and certain pathologic conditions that might cause pressure or traction on them

The literature seems to infer that venous hum occurs often in children but rather rarely in adults Auscultation over the lower neck on both sides supraclavicular region and upper chest revealed audible hums in 14% of 100 normal adults 40% of 100 women during the 8th month of pregnancy 61% of 78 adults with anemia whose packed cell volume was below 35% and 73% of 15 patients with hyperthyroidism These data showed that rapid blood flow is important in the genesis of the hum The high incidence in patients with anemia suggests that diminished blood viscosity is also important

The murmur is continuous in all instances with diastolic accentuation in some It is usually loudest and often rather sharply localized just above the sternoclavicular joint Hum is more frequent on the right and sometimes is bilateral The quality is usually roughly blowing occasionally rumbling

(3) Am Pra t. 6 342 345 M rch 1955

of 533 cases Patients were divided into four groups pure aortic *stenosis* (131) *aortic stenosis with insufficiency* (224) aortic and mitral stenosis with or without incompetence (149) and stenosis of the aortic mitral and tricuspid valves with or without insufficiency (29) Evidence indicated that in most patients aortic stenosis is primarily rheumatic in origin A history of rheumatic fever was obtained more often in patients with aortic stenosis and mitral stenosis than in those with aortic stenosis alone

Males predominated in the aortic cases females in the cases of trivalvular stenosis sex distribution was about the same in the cases of aortic and mitral stenosis

Average life span after onset of congestive failure was 22 7 months for pure aortic stenosis 28 9 months for aortic stenosis with insufficiency 56 4 months for aortic and mitral stenosis and 80 months for trivalvular stenosis Average age at death for the respective groups was 65 3 52 5 48 4 and 36 5 years Sudden death occurred in 23 4% of cases

Angina pectoris was present in 29 8% of the entire series Average life span after onset of angina was about four years regardless of the valves involved There was a small number of patients in the older age group and a larger number in the younger age group who had angina with essentially normal coronary vessels

Syncopal attacks were most frequent with pure aortic stenosis (20 6%) Average life span after onset of syncope was about three years

Left bundle branch block was much more frequent when the aortic valve alone was involved Auricular fibrillation was present in 10% of those with aortic stenosis alone and in 55% of those who also had mitral stenosis Prognosis was grave in cases of auricular fibrillation with aortic but no mitral stenosis and with normal blood pressure It was definitely better if hypertension was present Absence of left ventricular hypertrophy when only the aortic valve was involved indicated only a slight degree of aortic stenosis

The blood pressure level did not help in diagnosis The most constant finding was a systolic murmur Congestive *failure caused* the murmur to decrease and with recovery of compensation the murmur grew louder The aortic second sound was decreased or absent in most cases of pure aortic stenosis However it was normal or in[illegible] hy

A wide splitting of the first heart sound at the base of the heart is due to the addition of an extra sound in early systole during ejection of blood into the pulmonary artery or aorta and indicates dilatation of one of these vessels

Splitting of the second heart sound in the pulmonary area can be heard in most normal subjects during inspiration and is due to delay in closure of the pulmonary valve Abnormally wide splitting may be due to delay in the pulmonary component and this is caused by right bundle branch block increased right sided flow from left to right shunt or pulmonary stenosis In left bundle branch block the order of valve closure is reversed and the splitting is paradoxical decreasing on inspiration

Absence of the pulmonary component of the second sound is more common in older adults and is usually due to poor conduction of heart sounds because of emphysema A single second sound is found in severe pulmonary stenosis and in pulmonary atresia In pulmonary hypertension the second sound in the pulmonary area is extremely loud and may appear single on auscultation Complete absence of the aortic component of the second sound is rare being almost confined to cases of severe aortic stenosis and incompetence

The opening snap of mitral stenosis may be mistaken for the second component of a split second sound The snap is maximal at the lower left sternal edge and often well conducted everywhere The pulmonary component of the second sound is loudest in the second and third left spaces and is absent at the apex except in pulmonary hypertension The snap i maximal during expiration whereas the pulmonary sound is usually only obvious as a separate sound during inspiration

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HYPERTENSION

Studies on Control of Hypertension by Hyphex—*IV Levels of agents in urine and blood*—Because oral therapy of severe arterial hypertension with hexamethonium chloride and 1 hydrazinophthalazine (hyphex is a combination of these drugs) is highly effective H Mitchell Perry

and rather rarely humming Pitch is variable Venous hum is usually clearly audible but not loud though its intensity may increase to grade III in which case it is likely to be widely transmitted and associated with a thrill

The relation of venous hum to position phase of respiration and pressure is important in distinguishing it from other murmurs It remains constant during normal respiration but nearly always disappears with forced inspiration or expiration particularly with the Valsalva or Muller maneuver Venous hum is usually louder when the subject is sitting than when recumbent Lowering the head usually causes it to disappear slight turning of the head to the opposite side makes it louder and to the same side softer Extreme rotation in either direction often causes disappearance Compression of the internal jugular vein between the trachea and sternocleidomastoid muscle causes disappearance in nearly all instances Diagnostically the most important characteristics are absence of systolic accentuation and disappearance under some maneuver

Since venous hums were detected in one of every seven normal adults this sign alone has limited diagnostic value Its presence should however bring to mind anemia hyperthyroidism and perhaps anatomic abnormalities of the neck or upper mediastinum Its principal clinical significance lies in its superficial resemblance to other vascular and cardiac murmurs especially thyroid bruit and the murmur of patent ductus arteriosus

Splitting of First and Second Heart Sounds is discussed by Aubrey Leatham[4] (St George s Hosp London) The splitting of the first heart sound commonly found in healthy persons is generally thought due to slight asynchronism of ventricular contraction Phonocardiograms suggest that the first component of a split first sound is due to closure of the mitral and the second to closure of the tricuspid valve

Splitting of the first sound should be differentiated from an added auricular sound and from a presystolic murmur The latter in mitral stenosis is loudest at the apex and after exertion and is almost invariably associated with a loud first sound and a mid diastolic murmur The auricular sound has a lower pitch and a longer time interval

(4) La c t 2 60 614 S pt 1954

ing initial hospitalization unbenefited by the drug Thus of 68 treated patients whose disease had not progressed to uremia 3 died of complications of hypertension and 11 of other causes

Of the 28 patients who did not continue the treatment 25 died all of hypertensive complications The three survivors all with early malignant hypertension had papilledema and showed regression of the disease

There were 45 survivors followed for 24 months or more on continuous treatment All 14 patients with cerebral edema on admission recovered Hypertensive retinitis improved in all patients but those admitted in uremia Hypertension of most patients was controlled at reasonable levels About half of the 20 living patients with azotemia had normal or near normal nonprotein nitrogen values Proteinuria regressed or disappeared in all survivors There were four deaths of acute interstitial fibrosis of the lungs probably due to the hexamethonium ion In 22 autopsies all on treated patients with renal insufficiency renal arteriolar necrosis was found in 11 There were no deaths from congestive heart failure These studies demonstrate the possibility of control of severe hypertension with normal activity for a year to 36 months

Essential Hypertension Its Treatment with Rauwolfia Serpentina Benth Arnold Galambos[7] (New York) gave raudixin to 50 hypertensive patients In mild cases the average daily dose was 200 mg in severe cases two to three times as much was required After a few weeks to months when full effect was achieved the dose could be reduced

The systolic pressure became normal in every case of mild to moderately advanced essential hypertension but the response was not so uniform in the arterial type In two thirds of the severe chronic or rapidly progressive cases the systolic pressure fell to 150 mm Hg or below whereas in the others the systolic elevation was reduced by at least half of the excess over normal The diastolic pressure dropped to or below normal in all cases of mild or moderate hypertension and in 15 of the 20 chronic severe cases In some cases even on full maintenance dose after a while the blood pressure may increase again Increase of the dose may or may not overcome this situation

(7) A gi logy 5 449-460 Oct ber 1954

Jr Henry A Schroeder and John D Morrow[5] (Washing ton Univ) studied the therapeutic levels of these agents in blood and their rate of renal excretion

About 6% of a single oral dose of hexamethonium was excreted in the urine half within six hours On continuous oral doses the mean renal recovery was 3 5% whereas on continuous parenteral doses about 10 times as much was excreted Therapeutic concentrations in plasma averaged 0 37 mg /100 cc a level as high as 16 mg /100 cc was found in a constipated azotemic patient who recovered

Levels of 1 hydrazinophthalazine (apresoline®) were like wise measured The mean recovery of free drug in the urine was 2 9% of a single oral dose half appeared within five hours On continuous oral doses the mean excretion was 1 1% Approximately the same amount appeared when the drug was given parenterally Therapeutic plasma levels averaged 0 023 mg /100 cc At the beginning of treatment about half as much drug was excreted in the urine free as was bound to mercaptan with therapeutic responses the relative amount of free drug increased to more than half of the total The dihydrazine derivative was not recovered in the urine as such In two years no tolerance to the hypo tensive effect of hyphex has been observed

V Effects on course of malignant stage—Schroeder Morrow and Perry[6] report a rigorous test of the effect of hyphex in improving the prognosis of 106 patients with malignant hypertension Early malignant hypertension was present in 24 subjects with two of the three findings of hypertensive retinitis (papilledema hemorrhages exu dates) high fixed diastolic pressure diminution of renal function and proteinuria Of 18 who continued treatment two died both of nonhypertensive complications Of 31 patients with severe malignant disease (with aforemen tioned signs and all three manifestations of hypertensive retinitis) 23 continued treatment One died of a hyperten sive complication (cerebral arterial thrombosis) and four others of unrelated conditions In a third group 41 patients had superimposed renal insufficiency (azotemia) 27 con tinued therapy Two died in uremia five other deaths were unrelated to hypertension Ten uremic patients all died dur

(5) Am J M Sc 2 8 405-416 Oct be 1954
(6) Circ lat on 10 321 330 September 19 4

subacute stage of nephritis and one died from congestive heart failure

Blood pressure decreased slowly after a latent period of one to four hours after parenteral administration of reserpine and attained maximum depression in two to five hours Excessive hypotension was rare

Side effects were sedation bradycardia weakness dreams and conjunctival injection Muscle tremors and a Parkinson like syndrome developed after several days of treatment with large doses (5 10 mg every four to eight hours) These symptoms subsided after discontinuation of the drug

Treatment of Hypertensive Emergencies Use of Veriloid in Oil Intramuscularly proved practicable in 24 patients 11 of whom had malignant hypertension and 3 were uremic Ralph V Ford W R Livesay Charles Spurr and John H Moyer[9] (Baylor Univ) gave the corn oil preparation in an initial dose of 2 mg (usually at 24 hour intervals) with subsequent doses adjusted upward in 2 mg increments until a blood pressure response was obtained Thereafter 0 5 mg increments were used until an optimal blood pressure re sponse was obtained (reduction of recumbent blood pres sure to 150/100) A satisfactory hypotensive response was obtained in nearly all patients Average duration of the effect was 6 1 hours (as compared with 3¼ hours following aqueous veriloid® intramuscularly) and onset of action aver aged 114 minutes (average 15 minutes with aqueous veri loid® given intramuscularly) Optimal dose was 1 5 7 0 mg At this level nine patients had brief nausea or vomiting Symptoms of the hypertensive crisis were improved in 13 patients Two with uremia had progression of the renal lesion and one died No symptoms of cerebral or coronary insufficiency were apparent

Adjustment of the dose is critical but fairly reproducible results can be obtained in individual patients Although on set of action is slower than with aqueous veriloid® intra venously constant supervision is unnecessary during admin istration of the oily preparation and fewer injections are required than is necessary with intramuscular injections of the aqueous preparation

For treatment of hypertensive crises where constant

(9) Am Heart J 48 123 129 J ly 1954

Bradycardia developed in every case of hypertension associated with tachycardia and was the first effect of raudixin

Although the sedative effect of the drug is inconstant during the day the hypnotic effect is reliable during the night In every case the decrease in blood pressure was followed by physical and mental well being Side effects such as diarrhea weight gain or nasal stuffiness were slight No toxic reactions were observed

The good results without any toxicity warrant the ole use of rauwolfia preparations in hypertension

Parenteral Reserpine in Treatment of Hypertensive Emergencies is reported by Warren M Hughes John H Moyer and William C Daeschner Jr[8] (Baylor Univ) to be effective and safe on a short term basis

The first group treated included 10 patients with malignant hypertension and 4 with severe benign hypertensive cardiovascular disease Initially 2 5 or 5 mg reserpine was given intravenously or intramuscularly then a schedule was established depending on degree and duration of blood pressure reduction Dosage varied from 1 to 10 mg every 4-24 hours or longer Therapy was changed to the oral route when feasible All patients had a significant depression in blood pressure and in nine the maximal depression supine was to normal Six of the 10 with malignant hypertension recovered from the malignant phase and were regulated on oral therapy Uremia was present in four patients before therapy and three died one continued to have severe uremia Patients with severe benign hypertensive cardiovascular disease were regulated on oral therapy

In the second group of six patients with toxemia of pregnancy four had severe pre eclampsia and two had benign hypertensive vascular disease and associated pre eclampsia The same general procedure of administration was followed Normotensive levels were attained in all patients and all recovered There were no fetal complications

The third group was of eight patients of pediatric age with acute glomerulonephritis Doses of 50 100 μg /kg / day were given intramuscularly and intravenously Seven had significant reduction in blood pressure and six became normotensive Six patients recovered one progressed to a

(8) A M A Arch I t Med 95 563 57 Apr 1 1955

nett and Walter F Kvale (Mayo Found) report 15 cases found in 15 984 consecutive autopsies performed during 1928-51 In 3 cases the pheochromocytoma was listed among possible diagnosis whereas tumor was unsuspected in 12

The tumor in one case was classified as a malignant pheochromocytoma with metastasis the other 14 were classified as benign Eleven of the 14 patients had a history of hypertension hypertension was persistent in 9 and paroxysmal in 2 In three without a record of hypertension the pheochromocytoma was an incidental finding and apparently symptomless

Pheochromocytoma was associated with neurofibromatosis in one case This is the eleventh recorded instance of association of these two disorders Benign nephrosclerosis was present in five cases and malignant nephrosclerosis in only one No demonstrable nephrosclerosis was evident in nine

Death resulted from shock after incidental operations in five patients suggesting the extreme danger of operative procedures in the presence of pheochromocytoma Autopsy revealed cardiac hypertrophy in 10 patients and pulmonary edema in 5 In all but three patients the adrenal tumor was directly or indirectly the cause of death

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CORONARY DISEASE

Significance of Tietze's Syndrome in Differential Diagnosis of Chest Pain is discussed by William H Wehrmacher[3] (Northwestern Univ) The condition is a painful benign nonsuppurative swelling of the costochrondral or sternoclavicular junction of unknown etiology Foreign reports of over 100 cases indicate its importance in differential diagnosis of chest pain Wehrmacher summarizes four additional cases

Patients have ill defined recurrent pain in the chest in the area of tender nodular swellings The pain may seem like a heavy weight pressing on the chest or may be a vague soreness or tightness inducing the patient to breathe deep

(2) New Engl J Med 251 959 965 Dec. 9 1954
(3) J.A.M.A. 157 505 507 Feb 5 1955

supervision is not possible the authors recommend intra muscular injections of veriloid® in oil at 12 hour intervals with adjustment up or down in 0 5 mg increments until sat isfactory reduction of blood pressure without prohibitive side reactions Once the dose has been established the time interval may be adjusted to provide maximal hypotensive coverage

Treatment of Late Hypertensive Toxemia with Vasodila tor Agents Especially Protoveratrine O Kaser[1] reports on 100 patients with toxemia of pregnancy given protovera trine Maternal mortality rate was nil and infant mortality was 6 9% No causal relation could be established between medication and death In five of seven cases of eclampsia no convulsions occurred after therapy was begun In the other two there were one and four attacks respectively These relative failures were due to insufficient dosage Eclampsia did not occur in the 93 patients with mild or severe pre eclampsia

Elevated blood pressure was successfully reduced with protoveratrine given intravenously in 24 of 25 patients in tramuscularly in 47 of 53 and orally in 24 of 40 In most of the other patients more protoveratrine would probably have been more effective When blood pressure was reduced other signs and symptoms of pre eclampsia and eclampsia disap peared gradually Side effects were moderate and without danger Treatment had to be discontinued because of severe vomiting only once

Renal clearance studies revealed a transitory decrease of blood flow when the blood pressure was reduced rapidly Slow reduction improved the renal blood flow immediately in several cases In a few instances protoveratrine A and B were used without any advantage over the earlier form of protoveratrine

Kaser found protoveratrine superior to other conventional methods of treatment

Pheochromocytoma Study of 15 Cases Diagnosed at Autopsy Pheochromocytoma is a rare tumor and diagnosis is in most cases made at autopsy Numerous reports empha size its frequent association with either paroxysmal or sus tained hypertension Alexander M Minno Warren A Ben

(1) Schw i med W h sch 84 171 180 J n 30 1954

mimic serious organic disease and are usually very disabling. The initial link in the pathogenesis of the syndrome is hyperventilation with resulting acapnia which induces widespread biochemical neurovascular and neuromuscular changes These in turn evoke a psychic response of apprehension that accentuates and perpetuates the cycle Peripheral and perioral paresthesias are common together with muscle irritability and occasional tetany Symptoms referable to the cardiovascular system are the most frequent Precordial pain is common A characteristic triad of bloating belching and flatulence is often present and results from the concurrent aerophagia Anxiety tension apprehension and other psychic features are prominent

It is significant that overbreathing is often not immediately perceived by the patient and may not be recognized until after onset of the other symptoms Thus the dyspneic sensation may not precede awareness of other complaints Reproduction of symptoms by voluntary hyperpnea with an explanation and reassurance by the physician is beneficial and often will lead to disclosure of the emotional conflicts which form the background of the illness Typically the symptoms begin within a minute of hyperpnea but the maneuver should be carried on for as long as three minutes to demonstrate a full attack Frequently with deliberate overbreathing certain features of the spontaneous syndrome fail to appear Lewis believes that the presence of various stresses during the spontaneous attacks is responsible for these symptoms

[The frequency and importance of the hyperventilation syndrome merit strong emphasis The disorder not only is common in emotionally disturbed patients without organic cardiovascular disease but is frequently responsible for symptoms in patients who have organic cardiac disorders which are in themselves asymptomatic. The patient's knowledge that cardiac disease is present when coupled with unwise and unnecessary restrictions imposed by the physician may lead to an anxiety state which manifests itself through the hyperventilation syndrome Fear concerning heart disease frequently causes more suffering than does the heart disease itself—Ed]

Interplay of Coronary Vascular Resistance and Myocardial Compression in Regulating Coronary Flow was investigated by coronary sinus studies in dogs by Carl J Wiggers[5] Phasic changes in coronary sinus flow were registered by a differential manometer placed in a circuit which shunted coronary sinus flow into the superior vena cava

(5) Circulation Res 2 271 279 May 1954

ly It may radiate as a soreness into the shoulder arm or neck with intensity varying over a few hours or days The course is long with alternating remissions and exacerba tions Inclement weather respiratory infections anxiety and fatigue often aggravate the distress Recumbency often in creases pain

Tender bulbous or fusiform swellings involving the soft tissue cartilage and bone in the costochondral or sterno clavicular junctions are characteristic The overlying skin is not altered and moves freely over the mass No diagnostic x ray changes are apparent Inconstant pathologic altera tions from no changes to thickening of perichondrium mus cle fascia and ligaments around the costochondral junction and swelling of cartilage to resemble a nonmalignant tu mor are reported

Differentiation of Tietze s syndrome from neoplasms of the chest wall cancer of the breast or lung diseases of the heart pericardium and great vessels is of primary impor tance Also to be differentiated are chest deformity contu sion or inflammation of chest wall painful callus following rib fracture slipping rib traumatic intercostal neuritis ar thritis pulmonary embolism pneumothorax mediastinal emphysema presternal edema due to lymphatic obstruction from mumps or Hodgkin s disease and invasion of the chest wall by chronic granulomatous or neoplastic disease Treatment includes reassuring the patient of the benign character of the disease application of heat use of salicy lates and local infiltration of procaine

[There is an extremely common disorder which may or may not represent a mild form of this yndrome This common disorder is char acterized by pain in the chest with tenderness at the costochondral or chondrosternal junctions Localized pressure at the tender point repro duces the spontaneous pain in terms of quality and location although not always in terms of severity Thus benign condition in frequently con fused with angina pectoris Such confusion is especially common if the patient happens also to present some unimportant T wave changes in the electrocardiogram The combination of pain arising in the chest wall and unimportant ECG alterations frequently leads to a mistaken diagnosis of cardiac disease and the usual tragic sequence of events attendant upon such a diagnostic error —Ed]

Chronic Hyperventilation Syndrome Contrary to the general impression Bernard I Lewis[4] (State Univ of Iowa) finds that hyperventilation syndromes are common are gen erally chronic present diverse clinical pictures which often

(4) J A M A. 155 1 04-1208 J ly 21 1954

Jack Edwards[6] (Med College of Alabama) describes musculoskeletal chest pain encountered in 8 of 60 patients

Onset of the chest pain occurred two weeks after myocardial infarction in six of the patients and three and six months later in the other two The pain was located in the left *precordium in six and spread to the entire anterior chest* wall in two Postinfarction pain was in the same area as the pain of the acute infarction in half the patients Onset was gradual and pain lasted from 30 minutes to several days usually 1 or 2 hours It was a steady dull aching or pressing pain of mild to moderate intensity However in two it was so severe that opiates were required Episodes recurred intermittently for one month to three years

Pain was not related to generalized physical exertion but was likely to occur when the patient was fatigued and became worse on lying down in five patients especially if lying on the left shoulder Seven could relate either onset or aggravation of pain to a specific movement of the body or arm Six patients had localized muscle tenderness in the area of the pains but spontaneous pain could not be reproduced by pressure Nitroglycerin had no effect

Three patients had angina pectoris after myocardial infarction and two could not differentiate attacks of angina *until the exercise test separated the short lived anginal pain* from the prolonged skeletal pain Lack of specific relationship of pain to exertion absence of ECG changes during pain absence of response to nitroglycerin and reproduction by arm or body motion clearly differentiate skeletal pain from angina pectoris Reassurance that the pain is not serious local heat and analgesics allay anxiety about musculoskeletal pain and reduce its intensity

Treatment of Postmyocardial Infarction Shoulder Hand Syndrome with Local Hydrocortisone Herbert Berger[7] (Tottenville N Y) states that the shoulder hand syndrome is not uncommon following myocardial infarction The syndrome of pain in the shoulder referred to the hand accompanied by limitation of motion around the shoulder girdle and trophic changes in the hand resembling causalgia is believed to be initiated by a train of noxious impulses arising in the damaged heart muscle Trigger points in

(6) Am H rt J 49 713 718 M y 1955
(7) P tg d Med 25 508 511 J 1954

Pressures from the aorta and right ventricle were recorded by calibrated Wiggers optical manometers Coronary flow during a premature systole compensatory period and post compensatory beat was considerably less than that occurring during two normal beats and thus demonstrates the inefficiency of arrhythmia and its deleterious effect on ventricular blood flow

Anoxia caused a great increase in coronary sinus flow Dilatation of the coronary vessels accounted for a portion of this increment but the more forceful beat with its massaging action is far more effective in enhancing coronary flow Adenylic acid 10 mg intravenously produced a decline in arterial pressure and coronary vascular resistance but increased the coronary sinus flow by a third Epinephrine in small doses increased coronary vascular resistance as opposed to the effects of anoxia and adenylic acid but the increased force of ventricular contractions produced a net increase in coronary flow Aortic compression and pulmonary artery compression decreased coronary vascular resistance coronary flow however increased greatly during aortic compression but by contrast the augmentation of coronary flow observed during pulmonary artery compression was followed by a striking additional increase after release of the compression

Evidence obtained in these experiments that coronary flow increased during augmented activity of either the right or the left ventricle and evidence adduced from anatomy both favor the interpretation that the coronary sinus blood is not derived from the left ventricle alone but receives considerable contribution from the right ventricle The results also support the belief that the net effect of ventricular compression is to improve coronary flow (rather than to throttle it) and that whenever changes in vascular resistance occur they generally affect coronary flow less than the attendant changes in ventricular contraction

Musculoskeletal Chest Pain Following Myocardial Infarction Persistence of chest pain for months after disappearance of evidence of tissue destruction following myocardial infarction distinguishes it from acute infarction However when the pain begins in the first week after infarction differential diagnosis between skeletal pain and a second infarction or coronary insufficiency is di W L

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(6) Am Heart J 49 713 718 M y 1955
(7) P ig d Med 15 508 511 J 1954

the arm hand and shoulder may cause persisting pain after the source of myocardial difficulty has healed

Hydrocortisone in doses of 50 mg was injected into trigger points about the shoulder girdle in 18 patients Each patient experienced some or total relief of pain in 24 hours and gradually limitation of motion and trophic changes disappeared Most patients needed only one injection Since many patients had been treated previously by other methods it appears that this therapy is superior to other forms

Objective Evaluation of Coronary Vasodilator Drugs Henry I Russek Burton L Zohman and Virgil J Dorset[8] (U S P H S Staten Island N Y) compared the ability of 16 agents to modify the ECG response to standard exercise (Masters two step test) in patients with coronary disease

Glyceryl trinitrate (nitroglycerin) in therapeutic doses of 1/150 1/100 gr administered sublingually five minutes before the test had a strikingly favorable effect on response to exercise as recorded on the ECG of 45 of 60 patients Papaverine in doses of 1 2 gr intravenously or 3 8 gr orally decreased the abnormal ECG response in some patients but this benefit was not observed with the usual therapeutic doses

Of the agents tested pentaerythritol tetranitrate is the most effective drug available for prolonged prophylactic therapy in angina pectoris A 10 20 mg dose affords protection for four to five hours as judged from the two step test in most patients

Metamine® had little or no significant effect on the ECG response to exercise Paveril® improved the response in some cases but the action was not sustained and the effect never striking even with massive dosage Nitroglyn (glyceryl trinitrate in specially coated granules) in doses as high as 4/25 gr (9 6 mg) was followed by only slight to moderate improvement in exercise response in about half the patients The release of glyceryl trinitrate from this preparation is evidently too slow for clinical response The effects of aminophylline roniacol® priscoline® tetraethylammonium chloride octyl nitrite khellin heparin and dicumarol® were negligible when evaluated according to this method

(8) Am J M S 229 46-54 January 1955

Ethyl alcohol in 1 2 oz amounts failed to influence the exercise response although it prevented or reduced the severity of angina Alcohol should therefore be classified as a rapidly acting sedative and should not be prescribed as a coronary vasodilator drug Morphine is identical to alcohol in its effect on pain and in its failure to modify exercise response

Of the drugs tested only glyceryl trinitrate papaverine and pentaerythritol tetranitrate appear worthy of continued clinical use as vasodilators in management of angina

Treatment of Angina Pectoris with Cinchona Alkaloids Reports on the value of quinidine sulfate in angina pectoris led Joseph E F Riseman Lester A Steinberg and George E Altman[9] (Boston) to search for related drugs which would be equally effective but less toxic The efficacy of 12 preparations was studied in 32 patients These included placebos nitroglycerin five cinchona alkaloids (quinidine quinine cinchonidine cinchonine and cinchamidine) procaine amide chloroquine pentaquine chlorguanide and pentaerythritol tetranitrate Methods of evaluation included (1) comparison of clinical response with measurements of exercise tolerance under standard cold conditions and studies of the effect of medication on ECG changes induced by exercise (2) comparison of the value of cinchona alkaloids with ineffective placebos the very effective nitroglycerin and the slightly effective pentaerythritol tetranitrate and (3) analysis of results in those patients likely to respond to vasodilator therapy and those not likely to respond

Four cinchona alkaloids (quinidine quinine cinchonidine and cinchamidine) proved highly effective in some but not all patients Those most likely to respond to these alkaloids also responded well to nitroglycerin No toxic and few untoward effects were observed Quinidine and quinine are among the most effective of the drugs now available for treatment of angina pectoris Quinine is preferred because of low toxicity effectiveness and low cost It has little of the potential cardiotoxic effects of quinidine which is equally available but somewhat higher in price Quinidine is possibly somewhat more effective in angina than quinine

The effectiveness of the cinchona alkaloids in angina pectoris is due at least in part to a vasodilator action The

(9) Circulation 10 809 813 December 1954

quinoline ring is probably the portion of the molecule primarily responsible for the therapeutic effect

Effects of Diet on Blood Lipids in Man Particularly Cholesterol and Lipoproteins were studied by Ancel Keys Joseph T Anderson Flaminio Fidanza Margaret Haney Keys and Bengt Swahn[1] (Univ of Minnesota) Lipids exist in the blood serum as emulsions (chylomicrons) and as solutions of lipoproteins containing proteins cholesterol and other lipids Interest in relation to atherosclerosis is centered on cholesterol and beta lipoproteins which contain most of the cholesterol

Diet influences blood lipids in man and animals but great quantitative differences between species make it essential to study man himself to determine these effects Controlled experiments on healthy human subjects showed that the amount of lipid in chylomicron form in serum was practically independent of the concentration of cholesterol and lipoproteins The correlation between concentrations of alpha and beta lipoproteins was very low The data indicate that the effects of diet on each blood lipid should be considered separately

Dietary experiments showed that cholesterol per se even in large amounts or calories had little effect on serum cholesterol concentration but was markedly affected by the total fat content of the diet Studies on population samples of healthy men in different countries indicated direct relationship between content or proportion of fat in the diet and concentration of total cholesterol and beta lipoproteins This effect tended to be greater in middle aged than in younger men The average concentration of cholesterol in the serum of men in areas where diets are high in fats (40% of calories) as the United States and Sweden was 25 50% greater than in areas where diets are low in fats (20% or less of calories) as in Naples and among the South African Bantu

A significant effect of dietary fat level on serum cholesterol concentration is evident in man in a few weeks on a changed diet The effect tends to increase slowly thereafter it is most pronounced in comparisons of populations habitually living on different diets It is not known how

(1) Clin Chem. 1 34 52 Febru ry 1955

dietary fat intake exerts its controlling influence on blood lipids

Influence of Sex and Sex Hormones on Development of Atherosclerosis and on Lipoproteins of Plasma David P Barr[2] (Cornell Univ) states that although the extent of lipid deposit in most arteries differs little in men and women some precocity of its development in the coronary arteries of men is noted Angina pectoris coronary occlusion and myocardial infarction thus rarely occur in women before the age of 40 Arteriosclerotic disease of the vessels of the legs is also more common in men

The susceptibility of men and the relative immunity of young women to serious consequences of coronary and peripheral atherosclerosis is not satisfactorily explained by anatomic differences in the sexes or by any demonstrable variation in concentration of total lipids cholesterol or phospholipids Sex linked differences in distribution of lipoproteins can however be demonstrated by Cohn fractionation of plasma or by paper electrophoresis and ultracentrifugation Young men tend to have in their plasma a greater concentration of beta lipoproteins a smaller amount of alpha lipoproteins a higher beta alpha ratio and a larger content of S_f 10 20 lipoproteins Action of heparin in clearing alimentary hyperlipemia is less prompt in young men and the number of mast cells in their tissues is less than in young women None of these distinguishing features of sex are apparent in the aged becoming less prominent after the time of the menopause

Studies of conditions in the domestic fowl have shed some light on the nature of sex linked differences in development of atherosclerosis but species differences have made difficult the application of this knowledge to the problems of human atherosclerosis

Administration of gonadal hormones in man is accompanied by changes in distribution of lipids in the plasma Estrogen transforms the highly abnormal lipid pattern of myocardial infarction to a pattern similar to that of healthy young women Methyltestosterone on the other hand exaggerates the lipid abnormality of survivors of myocardial infarction and produces patterns similar to those of coronary

(2) J Ch on D 1 63 85 J uary 1955

quinoline ring is probably the portion of the molecule primarily responsible for the therapeutic effect

Effects of Diet on Blood Lipids in Man Particularly Cholesterol and Lipoproteins were studied by Ancel Keys Joseph T Anderson Flaminio Fidanza Margaret Haney Keys and Bengt Swahn[1] (Univ of Minnesota) Lipids exist in the blood serum as emulsions (chylomicrons) and as solutions of lipoproteins containing proteins cholesterol and other lipids Interest in relation to atherosclerosis is centered on cholesterol and beta lipoproteins which contain most of the cholesterol

Diet influences blood lipids in man and animals but great quantitative differences between species make it essential to study man himself to determine these effects Controlled experiments on healthy human subjects showed that the amount of lipid in chylomicron form in serum was practically independent of the concentration of cholesterol and lipoproteins The correlation between concentrations of alpha and beta lipoproteins was very low The data indicate that the effects of diet on each blood lipid should be considered separately

Dietary experiments showed that cholesterol per se even in large amounts or calories had little effect on serum cholesterol concentration but was markedly affected by the total fat content of the diet Studies on population samples of healthy men in different countries indicated direct relationship between content or proportion of fat in the diet and concentration of total cholesterol and beta lipoproteins This effect tended to be greater in middle aged than in younger men The average concentration of cholesterol in the serum of men in areas where diets are high in fats (40% of calories) as the United States and Sweden was 25 50% greater than in areas where diets are low in fats (20% or less of calories) as in Naples and among the South African Bantu

A significant effect of dietary fat level on serum cholesterol concentration is evident in man in a few weeks on a changed diet The effect tends to increase slowly thereafter it is most pronounced in comparisons of populations habitually living on different diets It is not known how

(1) Cli Chem. 1 34 3 F bruary 1955

cholesterol in the development of atherosclerosis prompted search for direct proof that metastatic calcium can be re moved from the body by a safe practical method The che lating compound ethylene diamine tetra acetic acid (EDTA) which can form strong soluble complexes with cations in solutions that can then be readily excreted in the urine was chosen for the study

METHOD—The compound was administered intravenously as a solution of 5 Gm EDTA in 500 cc of 5% glucose or normal saline The intravenous drip was regulated to total infusion in 1½ 3 hours Several patients were given 10 Gm EDTA in 1 000 cc but for pro longed treatment 5 Gm /day was most satisfactory A total of 12 20 infusions was given in a series then omitted for two or three weeks

The fewest infusions administered to a patient were 10 the most 100 average 50 More than 1 200 infusions of 5 or 10 Gm EDTA were given 22 patients with nephrocalcino sis rheumatoid arthritis diabetic neuroretinitis peripheral vascular disease angina pectoris indolent ulcer with exten sive calcium metastasis in the neck neuromuscular diseases calcified mitral stenosis and otosclerosis

Comparison of serum calcium levels immediately before and after administration of the disodium salt of EDTA shows no significant change The explanation is that under the conditions of this study the homeostatic mechanisms of the body were able to maintain normal serum calcium lev els by replenishing the amounts lost through EDTA admin istration from areas of metastatic calcium The EDTA which may be present in the serum must be destroyed by wet ashing before a reliable estimation of calcium content can be made by the oxalate method

Toxic effects of EDTA administration include burning sensation above the site of injection nausea abdominal cramping and toxic reactions on skin and mucous mem branes in the form of erythematous scaly and exfoliative dermatitis Following oral administration of 25 74 mg py ridoxine daily incidence and severity of toxic reactions were greatly reduced All symptoms subsided rapidly when therapy was terminated

atherosclerosis in individuals whose plasma previously showed no lipid abnormalities Contrary to experience in *the chick administration of androgens with estrogens ob*literates the chemical effects of estrogens

The accumulated clinical and experimental evidence leaves little doubt that sex is a potent factor in the development of atherosclerosis and that its influence is hormonal and accompanied by changes in distribution of lipids in plasma

Lowering of Serum Cholesterol by Administration of a Plant Sterol (beta sitosterol) was demonstrated by Maurice M Best Charles H Duncan Edward J Van Loon and Joan D Wathen[3] (Louisville Ky) in nine subjects who remained on an unrestricted diet Before the preparation was administered two had serum cholesterol levels within normal range and the others had hypercholesteremia Beta sitosterol was given orally in doses of 5 6 Gm immediately before meals Placebos with double blind control were used in the study which was of *13 29* weeks' duration Duplicate determinations of serum cholesterol were made weekly with each of three methods The reduction of total serum cholesterol ranged from *6.7* to *20%* of the control levels No tendency to escape was noted Following placebo administration values consistently rose

In some as yet uncertain way sitosterol which is not absorbed in the bowel interferes with absorption of endoge*nous and exogenous cholesterol The ratio of serum* total cholesterol to lipid phosphorus was reduced largely by virtue of reduction of total cholesterol In three subjects so tested there was a reduction in the atherogenic S_f 10 100 classes of lipoproteins

The preparation is not unpleasant and has no toxic effects in the dosages used Dietary reduction of serum cholesterol is tedious and difficult perhaps this method may be effective in causing sustained lowering of cholesterol in atherosclerotic conditions

In Vivo Dissolution of Metastatic Calcium An Approach to Atherosclerosis is discussed by Norman E Clarke Charles *N* Clarke *and Robert E Mosher*[4] *(Providence* Hosp Detroit) A possible interrelationship of calcium with

(3) Circulation 10 201 206 August, 1954
(4) Am. J M Sc 229 142 149 February 1955

effect had been achieved If the patient required 1 2 mg or more full digitalization was carried out

The result in one test was uncertain and one patient died Results in 12 indicated that the patients could profit from more digitalis in either full or partial dosage and in 7 that digitalis was contraindicated Although the findings frequently failed to be in accord with clinical impressions the patient s subsequent course corroborated the conclu sions of the test

Of the 12 patients requiring digitalis 9 were on main tenance doses 2 had received no digitalis and it was uncer tain whether one had taken any Of the seven who did not require digitalis three had digitalis intoxication not rec ognized on clinical grounds

Acetyl strophanthidin accelerated the death of one pa tient terminally ill with left sided and right sided failure unresponsive to all measures by causing ventricular tachy cardia and later fibrillation

Treatment of Incapacitated Euthyroid Cardiac Patients with Radioactive Iodine Summary of Results in 879 Pa tients with Angina Pectoris or Congestive Failure in 46 Clinics is reported by Herrman L Blumgart A Stone Freedberg and George S Kurland[6] (Boston) Probably less than 5% of patients with angina pectoris or congestive fail ure remain disabled despite all available measures It was thought that hypothyroidism induced by radioactive io dine may alleviate congestive failure and angina pectoris by lowering the total metabolism of the body which in turn would so reduce the systemic requirements as to be within the limit of cardiac reserve

Patients with angina pectoris who may be expected to benefit most from the treatment are those whose disease has been relatively stationary or only slightly progressive for one or more years Patients with congestive failure should show evidence of some cardiac reserve such as improve ment on bed rest or with the use of diuretics and digitalis They should be alert and emotionally stable Radioactive io dine is contraindicated in patients with recent angina pec toris or rapidly progressive cardiovascular disease

Patients in the euthyroid range should receive an initial

(6) T A. Am Phy i n 67 86 93 1954

CONGESTIVE FAILURE

Current Concepts in Digitalis Therapy Bernard Lown and Samuel A Levine[5] (Harvard Med School) state that the variation of cardiac response to digitalis in any one patient the frequency of conditions in which under and over digitalization are indistinguishable and the similarity of paroxysmal atrial tachycardia with block to many nondigitalis induced arrhythmias have made necessary a procedure for determining the digitalis status of cardiac patients A digitalis tolerance test is described that is based on biologic assay of myocardial sensitivity to a rapid acting digitalis like drug acetyl strophanthidin the effect of which is achieved within several minutes and dissipated rapidly The test has been carried out 20 times on 18 patients with congestive heart failure whose digitalis status was doubtful or in whom myocardial sensitivity to the drug was believed to be increased

TECHNIC—Two ampules each containing 0 6 mg acetyl strophanthidin were diluted to 20 cc in 5% glucose and water If the patient had received little or no digitalis 0 3 mg or 5 cc. of the solution was given intravenou ly every five minutes until a therapeutic effect or a mild toxic response was achieved In the presence of possible digitalis intoxication the interval doses were increased to 10 minutes or the first two doses were reduced to 0 15 mg If an arrhythmia probably due to digitalis was present potassium was given first and if ineffective was followed by a tolerance test The ECG was continuously observed With onset of evidence of intoxication nausea excepted the test was stopped If the toxic pattern consisted of ventricular premature beats small amounts of procaine amide were given intravenously until all extrasystoles had disappeared

Interpretation of the test was based on amount of acetyl strophanthidin required and on the qualitative respon e If toxicity developed after the first injection of 0 15 or 0 3 mg overdosage was presumed and no further digitalis was administered Toxicity following injection of 0 6 mg without any therapeutic effect was regarded as a sign of adequate digitalization When therapeutic action occurred after injection of 0 6 or 0 9 mg fractional doses of one of the commonly used digitalis preparations were given until the same

(5) New England J Med 250 866 874 May 20 1954

in the unfavorable group (classes III and IV) Surgery for rheumatic valvulitis should probably not be done during pregnancy

Effect of pregnancy on the life course of women with congenital heart disease is not well established There appears a slight tendency for some defects to be inheritable Dissection of the aorta occurs more frequently during pregnancy than can be expected by chance There is need for investigation of the effect of pregnancy on the aorta Mobilization of cholesterol may predispose to dissection Pregnancy has an unfavorable effect on subacute bacterial endocarditis and may aggravate essential hypertension Pure pre eclampsia or eclampsia on the other hand apparently does not cause heart disease

Although there is a lightening of the increased cardiac load during the last month of pregnancy it is important to recognize the profound changes that take place immediately after emptying of the uterus These include a sudden load on the maternal cardiovascular pulmonary systems perhaps partially due to an abrupt decrement in vital capacity consequent to suddenly decreased intra abdominal pressure

More study is indicated concerning circulation during pregnancy delivery and puerperium and the effects of circulating hormones on the cardiovascular system

Management of the Pregnant Patient with Cardiac Disease has improved so that many women may have successful pregnancies according to William Horowitz[8] (New York Med College) Interruption of pregnancy is rarely indicated for cardiac reasons except with tight mitral stenosis increased pulmonary pressure active rheumatic fever increasing hypertension and subacute bacterial endocarditis If necessary pregnancy should be terminated as early as possible after cardiac compensation has been restored Unless there are compelling obstetric indications interruption should not be attempted after the sixth lunar month

In antepartum care a low salt diet limitation of weight gain to 20 lb supplementary vitamins calcium and iron to prevent or control anemia avoidance of heavy physical exertion extra rest control of infection and frequent examinations are essential Onset of failure may be heralded

(8) New England J Med 252 511 515 Mar 31 1955

dose no larger than 20 mc and only half of this if attacks of angina pectoris occur at bed rest Usually three doses are given at weekly intervals As complicating hypermetabolism may occur during the second or third week after treatment patients with severe angina should be at rest during that time At two month intervals single doses are given until hypothyroidism develops Except for a few clinics in which large doses have been given with resulting hyperthyroidism thyroiditis has not been a serious problem Mild transitory thyroiditis occurs in about one third of the patients With improvement in cardiac symptoms usually two to six months after initiation of therapy 6-30 mg thyroid is given to control discomfort of myxedema

In 46 clinics 879 patients with intractable angina pectoris or congestive failure were treated with radioactive iodine About 75% with angina pectoris showed worthwhile improvement half of whom showed marked improvement and half a good result About 60% with congestive failure showed worthwhile 17% marked and 46% moderate improvement

Induced hypothyroidism does not retard progression of the underlying pathologic process It is not curative but palliative and an adjunct to routine treatment

[*It is the editor's opinion that this form of treatment is very rarely* needed in patients with angina pectoris Most such individuals can be restored to something approaching a reasonably normal life by the vigorous use of nitroglycerin and a program of gradually increasing walking The walks should be taken at the height of the nitroglycerin effect

In patients with congestive failure who remain incapacitated despite all other measures radioiodine appears to be decidedly worth a trial The results while sometimes disappointing are most gratifying in certain instances —*Ed.*]

Cardiovascular Problems in Pregnancy are chiefly concerned with maternal and infant death rates risk of immediate invalidism and whether maternal heart disease injures the infant Burton E Hamilton[7] states that in rheumatic heart disease the maternal mortality rate is only slightly increased particularly for 'favorable' patients (*New York Heart Association classes 1 and 2*) *Age over 35* also increases the mortality but parity is apparently irrelevant In favorable patients treatment of the heart disease has *impressively* reduced maternal deaths Infant mortality is about normal although it may be as high as 3 % or more

(7) Circulation 9 922 933 June 1954

due to dilatation interstitial edema of the myocardium and serous myocarditis or perhaps actual hypertrophy It may occur in the absence of hypertension is generally associated with heart failure and may be caused by acute hypervolemia The commonest ECG changes in acute glomerulonephritis are low or inverted T waves in lead I and precordial leads These resemble the changes occurring with overdosage of DCA and may reflect fluid and electrolyte metabolic abnormalities Actual failure of the heart may occur without previously existing myocardial disease and often responds strikingly when diuresis sets in Slowly rising blood pressure may herald heart failure reduction by antihypertensive agents may block impending disaster

In acute renal failure with anuria and renal insufficiency cardiac failure is again the commonest cause of death Hypervolemia perhaps plays a role and fluid overload should be scrupulously avoided Potassium intoxication another common cause of heart disease in renal insufficiency may be aggravated by hyponatremia and acidosis It is treated by administration of insulin and glucose to drive the potassium into the liver and muscle cells cation exchange resins and various dialyzing technics

The heart is usually involved in chronic renal disease in which concurrent hypertension is often associated with coronary arteriosclerosis Treatment of the hypertension though hazardous may be at least temporarily successful Concurrent anemia can be partially corrected with packed red cells Uremic pericarditis occurs in most cases of *chronic renal insufficiency although it is usually asymptomatic* In some cases there is a characteristic pulmonary uremic edema with butterfly like opacities fanning out from the hilar regions on x ray Oliguria proteinuria and azotemia may be due to congestive heart failure per se or to heart failure with chronic renal disease urinary specific gravity and other urinary findings indicate their cause Treatment of heart disease occurring with chronic renal disease must be correlated as well as possible with the diminished ability to excrete drugs

Management of Congestive Heart Failure Designed to Avoid Serious Disturbances of Electrolyte and Water Balance is described by Donald W Seldin[1] (Southwestern Med

(1) A.M.A Arch. I t. Med. 95 385 399 M h 1955

by rapid weight gain due to salt retention and elevation of pulse above 110 and of respirations above 24 Treatment is the same as for other patients with congestive failure On set of cardiac failure during gestation converts a favorable case to a poor risk with similar indications for abortion After the sixth month the patient should be maintained on digitalis a low salt diet ammonium chloride and mercurial diuretics as indicated preferably in the hospital If cardiac reserve is low patients are digitalized prophylactically before delivery

Arduous protracted labor or difficult forceps delivery must be avoided In problem cases and in coarctation or dissection of the aorta cesarean section is specifically indicated Analgesics and hypnotics may be used during the first stage of labor and anoxia must be avoided If pulse and respiratory rate rise 1 6 mg (8 cc) lanatoside C should be given immediately The second stage should be made as short as possible without undue manipulation A decompensated patient in labor should be kept semiupright and given oxygen continuously Pitocin® may be given after delivery except in cases of angina pectoris A tight abdominal binder should be applied The head of the bed should be elevated on blocks so that neck vein distention just disappears Even the patient with favorable cardiac disease should be kept in bed for at least a week with precautions taken against thrombosis Lactation should be suppressed

The Heart in Renal Disease may be implicated secondarily by changes produced by primary renal disease or concurrent disease of the heart may complicate therapy Harry A Derow[9] (Harvard Med School) summarizes diseases of the heart encountered in the presence of renal impairment and renal insufficiency

In acute glomerulonephritis the commonest cause of death is heart failure The important manifestations of cardiovascular disturbances—hypertension cardiac enlargment ECG abnormalities and heart failure—may be difficult to classify as primary or as consequences of kidney disease Hypertension a common symptom is of undetermined origin its role in the development of heart failure or heart disease is variable Cardiac enlargement which often appears with in the first week or two of acute glomerulonephritis may be

(9) Circulation 10 114 128 J ly 1954

treatment of edema has doubtful value as a diuretic in heart failure Its principal function (in 2 5 Gm daily doses the day before and for two days after mercury injection) is to enhance sodium excretion and to prevent alkalosis Ammonium chloride should be given cautiously if at all to patients with renal or liver disease or primary pulmonary insufficiency

Except in cor pulmonale acetazoleamide is only mildly effective as a diuretic in congestive heart failure A modest initial diuretic response occurs but continuous administration usually fails to elicit further sodium loss Its tendency to produce high chloride acidosis used to potentiate mercurial diuretics can be enhanced by simultaneous administration of small amounts of ammonium chloride

Effect of Ganglion Blocking Agents in Congestive Heart Failure Charles R Shuman Norman Learner and John H Doane Jr (Temple Univ) used tetraethylammonium bromide (TEA) and hexamethonium iodide (HMI) which have been demonstrated to interfere with transmission of sympathetic impulses by preventing the action of acetylcholine on ganglion cells and of parasympathetic impulses by interfering at the effector cells in 21 patients with heart failure and 7 others without failure All patients in failure were dyspneic and most had hepatic congestion and peripheral edema After base line determinations the blocking agents were given by slow injection through the adapter of an intravenous drip apparatus The dose of TEA was 150 500 mg and of HMI 12 5 50 mg depending on the patient s size and severity of heart disease

The most impressive effect was prompt relief of dyspnea in all patients in failure lasting 24-48 hours The elevated venous pressure dropped precipitously simultaneously with a drop in arterial pressure Return of arterial pressure to the pre injection level was accompanied by rise of venous pressure but not to the previous abnormal levels Most of the controls not in failure experienced the same fall in arterial and venous pressures Digital skin temperature changes and plethysmographic data on digital blood flow were widely variable Five of 11 heart failure patients had no change in skin temperature or plethysmographic readings 4 others

(2) Am Heart J 47 737 744 May 1954

School) Digitalis postural changes and bed rest are principal measures used to correct the basic disequilibrium in heart failure Low salt diets and cation exchange resins diminish salt intake and renal excretion of salt may be promoted by mercurials ammonium chloride acetazoleamide potassium salts and xanthines

Rigorous restriction of dietary salt prevents or retards additional fluid accumulation *Potential* hazards can be averted by periodic clinical and laboratory examinations to detect signs of azotemia and hyponatremia Cation exchange *resins can promote excretion of large quantities of sodium* in feces and reduce or even eliminate the need for mercurials For supplementary diuresis the acidifying effect of resins enhances mercurial effect

When digitalis rest salt restriction and resins are ineffective in removing edema mercurial diuretics preferably by subcutaneous and intramuscular injections promote salt excretion by inhibiting renal tubular reabsorption of sodium A test dose of 0 5 cc should be given especially in elderly patients or those with renal insufficiency and not over 2 cc should be injected at one time The drug should be injected in the morning no oftener than two or three times weekly

Hypochloremic alkalosis should be suspected in any patient who becomes refractory to the action of mercury Responsiveness can be restored by ammonium chloride orally or intravenously sometimes combined with acetazoleamide Potassium deficiency is usually corrected by 3-4 Gm KCl daily for several days and can often be prevented by 2 Gm KCl given on the day of and the day after mercury injection Respiratory acidosis must not be mistaken for metabolic alkalosis because ammonium chloride therapy may be hazardous since the decompensation of acidosis may increase susceptibility to CO narcosis *Mercurial refractoriness* may also be caused by hyponatremia often accompanied by anorexia lethargy mental confusion azotemia and hypotension Correction by hypertonic saline (3 5%) may increase responsiveness *to mercury Aminophylline* 0 48 0 72 Gm intravenously may restore responsiveness in some patients with a low glomerular filtration rate

Ammonium chloride the principal acidifying salt *for*

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(2) Am. Heart J 47 737 744 M y 1954

had a fall in skin temperature and 2, a rise By contrast the skin temperature rose in six of the seven without failure This suggests that the neurogenic constrictor impulses in viscera and muscles are the principal sites of blockade in patients with congestive failure Vital capacity measurements in 10 patients in heart failure who received hexamethonium showed the average change to be about a one third increase

The beneficial effect of autonomic blockade in congestive failure may result from pooling of blood beyond the central cardiopulmonary area The release of neurogenic reflexes increasing arteriolar and venular tone will reduce the work load of the left ventricle and decrease the elevated venous filling pressures of the right heart

Treatment of Congestive Heart Failure and Anginal Syndrome with Choline Theophyllinate was studied by Robert C Batterman Arthur J Grossman Julius Schwimmer and Alan L Blackman[3] (New York Med College) in 68 patients Medication was given orally in doses of 50-400 mg three or four times daily 200 mg being the most satisfactory dose The drug was given for 14 days to 74 weeks

Twenty four ambulatory and 21 hospitalized patients had congestive heart failure With few exceptions they did not respond to daily maximum tolerated doses of a digitalis preparation and parenteral administration of mercurial diuretic was necessary for control of diminished cardiac reserve Results of therapy with choline theophyllinate were in three categories The first no longer needed diuretics indicating complete control of the symptoms of congestive heart failure in the second diuretics were needed infrequently and the third had decrease of at least 50% in need for diuretics Any effect less than this was considered insignificant According to these rigid criteria, effective response was attained in 28 of the patients (62%) The diuretic response and relief of symptoms were gradual in onset and several days were required before maximum results were evident

Thirty two patients 30 ambulatory and 2 hospitalized were treated for the anginal syndrome Nine were also treated for congestive heart failure and were included in the first group All had a classic history of substernal midline

(3) J A M A 157 234 237 Jan. 15 1955

pain with or without radiation lasting a few minutes occurring with exertion and relieved promptly by glyceryl trinitrate therapy The same criteria for effectiveness were used as in congestive heart failure Satisfactory relief and control were obtained in 23 (72%) There was complete freedom from chest pain in nine six patients required only occasional therapy with glyceryl trinitrate and in eight glyceryl trinitrate requirements were decreased by more than 50%

Results with choline theophyllinate indicate that the disadvantages of xanthine therapy are abolished or minimized Better absorption and higher blood level with choline theophyllinate and greater solubility and decreased toxicity compared with aminophylline are found Even after 75 weeks of continued administration tolerance was not noted

Errors in Recognition and Treatment of Heart Disease R Bruce Logue and J Willis Hurst[4] (Emory Univ) state that diagnosis of angina pectoris depends on the history and not on ECG abnormalities In elderly patients anginal discomfort may occur only after meals (indigestion) accompanied by sweating or weakness

The pain of emotional tension simulates that of coronary disease However it lasts for hours or days is unrelated to effort and is unrelieved by nitroglycerin Pain in pulmonary hypertension may be indistinguishable from that of coronary disease Nitroglycerin may fail to give relief but aminophylline given intravenously may cause dramatic improvement The pain in gallbladder disease degeneration of a cervical disk and dissecting aneurysm may suggest heart disease

Fever of more than 2 degrees F does not occur with uncomplicated heart failure If dyspnea or wheezing are present and there is no evidence of coronary hypertensive or valvular heart disease and heart size is normal a pulmonary origin should be suspected Peripheral edema is usually not due to heart failure if heart size is normal except in cor pulmonale and constrictive pericarditis Interstitial pulmonary congestion may be present without rales and is evident on x ray study Syncope may be caused by Stokes Adams attacks aortic regurgitation or stenosis or paroxysmal tachycardia

(4) Circulation 10 920 93 December 1954

The predominant apical location of murmurs serves to differentiate rheumatic from congenital lesions in which the murmurs are largely basal or midsternal Diastolic rumble at the apex may occur in acute rheumatic fever and may disappear as activity subsides A single ECG is inadequate for recognition of rheumatic fever Many childhood diseases produce a prolonged P R interval

Aortic stenosis is the commonest valvular lesion after age 50 Its murmur is usually heard in the aortic area and is transmitted to the neck The aortic second sound is normal in about half the cases and a small pulse pressure is a late and infrequent sign A marked degree of left ventricular hypertrophy with strain pattern in the ECG without hypertension as well as the association of angina pectoris and syncope should suggest aortic stenosis

The commonly expected findings of petechiae splenomegaly hematuria and leukocytosis occur in less than 50% of cases of bacterial endocarditis Occasionally even fever is missing

Constrictive pericarditis should be suspected when increased venous pressure hepatomegaly ascites and edema cannot be readily explained In most cases the heart is of normal size or is enlarged

Besides the characteristic signs pulmonary embolism may be recognized by acute pleurisy syncope episodes of weakness and sweating tachycardia out of proportion to fever paroxysmal auricular fibrillation refractory heart failure and repeated attacks of supposed coronary occlusion

Unusual Forms of Heart Disease Howard B Burchell[5] (Mayo Clinic) classifies unusual cardiologic cases in which the cardiologist might be at loss for a diagnosis as follows (1) rare anatomic conditions such as Ebstein s malformation of the tricuspid valve traumatic rupture of a valve and primary neoplasm (2) heart affected as an integral part of a general disease as in amyloidosis lupus erythematosus scleroderma and hemochromatosis (3) cardiac complications of other disease e g diphtheria, purulent pericarditis anemias thyrotoxicosis arteriovenous fistula and myocardial metastasis (4) conditions precipitating or accelerating development of more usual forms of acquired heart disease such as xanthomatosis obesity and myxedema (5) con

(5) Circulation 10 574 579 October 1954

ditions mimicking primary heart disease e g thrombosis or involvement of the inferior vena cava by tumor

In Ebstein s malformation the right ventricle is unable to impel an adequate quantity of blood into the lungs be cause of a misplaced deformed tricuspid valve Tricuspid insufficiency may be present Characteristics of the syn drome are cardiac enlargement clear lung fields and low pressure in the right heart The ECG frequently shows right bundle branch block Most cases are associated with atrial septal defect with resulting mild to moderate cyanosis

In primary amyloidosis the heart is often seriou ly af fected and failure predominates The picture may simulate that of chronic constrictive pericarditis Diagnosis is best confirmed by liver biopsy

Heart failure may be the presenting symptom in hemo chromatosis The quantity of pigment in the myocardium at times has seemed sufficient to cause heart failure How ever other contributing factors such as coronary disease accelerated by the diabetic state or possibly anemia from bleeding esophageal varices should be suspected

Mitral stenosis may be simulated by acquired stenosis of the pulmonary veins and left atrial tumor most commonly myxoma Aortic sinus aneurysms frequently rupture into the right side of the heart and a continuous bruit like that of patent ductus arteriosus results Sudden onset of weak ness or dyspnea coincident with the appearance of such a bruit is clinically diagnostic

Idiopathic acute pericarditis is relatively common Peri cardial biopsy should be considered to rule out granulom atous or neoplastic disease if reversion to health or of the cardiac silhouette to normal size is delayed

Occasionally heart failure is related to systemic arterio venous fistula

Endocardial Fibroelastosis Factor in Heart Disease of Obscure Etiology Study of 20 autopsied cases in children and adults is presented by Wilbur A Thomas Raymond V Randall Edward F Bland and Benjamin Castleman[6] (Har vard Med School) In a review of 10 000 autopsies they found 24 cases of chronic heart disease with hypertrophy of uncertain etiology 20 with abnormal degrees of fibroelasto sis Of the other four two showed hypertrophy and dilata

(6) N w E gla d J M d. 251 327 338 A g 26 1954

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(5) Circulation 10 374-5 9 October 1954

diagnosed long before overt signs of right ventricular failure are evident A distinct clinical picture characteristic radiologic findings and ECG changes assist greatly in recognition of this disease Signs and symptoms of the early pulmonary stage are cough cyanosis dyspnea clubbing of fingers diminished chest expansion and increased anteroposterior diameter fixation of diaphragm and polycythemia Outstanding features of the later cardiac stage are engorged neck veins enlarged and tender liver generalized edema and increased venous pressure Regular sinus rhythm and normal blood pressure are usual in chronic cor pulmonale but occasionally there is ectopic rhythm Accentuation of the second pulmonic sound is constant and a systolic murmur is often audible In the compensated stage these two findings plus an increase in cyanosis and polycythemia are often the only signs of cardiac involvement

Circulatory function is normal in uncomplicated pulmonary disease in the early stages Incipient right heart failure shows a normal initial venous pressure with a varying rise during compression of the right upper abdominal quadrant In frank isolated right heart failure initial venous pressure is high with considerable rise on right upper quadrant compression a prolonged arm to lung circulation time and relatively normal lung to tongue time The characteristic x ray picture indicates hypertrophy of the right ventricle and dilatation of the pulmonary artery In early stages ECG changes may be minimal In later stages the typical ECG pattern of right ventricular hypertrophy is seen

Successful therapy of cor pulmonale depends on proper understanding of physiopathologic factors In pulmonary emphysema aerosolized bronchodilators oxygen and antibiotics are effective When hypercapnia develops with anoxia or the two are present concomitantly long continued artificial respiration with oxygenation has been suggested When frank congestive heart failure appears digitalis low salt diet diuretics and phlebotomy are recommended

Role of Potassium in Prevention of Alkalosis was studied by Robert E Cooke William E Segar Claude Reed Donnell D Etzwiler Martin Vita Saul Brusilow and Daniel C Darrow[8] (Yale Univ) Rats were given a diet containing negligible amounts of sodium potassium and chloride

(8) Am J M d 17 180 195 A g t 1954

tion without other distinguishing characteristics one had no hypertrophy but a tremendously dilated paper thin right ventricle and one a severe giant cell myocarditis

The 20 cases with endocardial fibroelastosis were divided into three groups infantile (under age 2) childhood (age 2 16) and adult (over 16) A congenital etiology is pro posed also for the adult group despite the time lag between birth and onset of symptoms, because the hearts are mor phologically identical with and the clinical picture similar to those in the earlier age groups

Endocardial fibroelastosis is not specific but is seen as a secondary feature in severe coronary sclerosis with myo cardial infarcts and occasionally beneath the valve in aortic or mitral regurgitation It is a constant feature in children who have an anomalous coronary artery arising from the pulmonary artery However it is not a secondary feature of congestive heart failure regardless of cause

Beriberi heart disease myocarditis, East African endomy ocardial necrosis and collagen disease can be differentiated from endocardial fibroelastosis by clinical and pathologic features

For the correlation of the severe clinical symptoms of endocardial fibroelastosis with the relatively unimpressive morphologic changes a number of theories have been ad vanced One is that the thickened endocardium interferes with proper contraction and relaxation of the heart as a thickened pericardium does in constrictive pericarditis An other possibility is that the thickened endocardium inter feres with the proper conduction of contraction impulses That the thickened endocardium interferes with the blood supply to the underlying muscle is a third possibility Prob ably all these factors play a part

Effect of Chronic Pulmonary Disease on the Heart Max well L Gelfand[7] (New York) defines cor pulmonale as heart disease in which right ventricular hypertrophy re sults solely from diseases of the lungs pulmonary vessels or thoracic cage Its etiology is manifold and incidence varies The ratio of males to females is 4 1 Increased pres sure in the pulmonary circuit is probably due mainly to anoxia and anatomic obliteration of the pulmonary vascular bed With cardiac catheterization cor pulmonale can be

(7) Am J Su g 89 245 51 January 1955

kidney function or of marked oliguria such salts should be administered only with the greatest caution —Ed.]

Clinical Tests of Simple Method of Estimating Cardiac Stroke Volume from Blood Pressure and Age Isaac Starr[9] (Univ of Pennsylvania) compared the cardiac output determined by the Fick ethyl iodide nitrous oxide T 1824 and acetylene methods in about 400 reports by various authors with that obtained by applying to these authors data formulas for estimating stroke volume based on blood pressure and age Although there are inherent limitations in comparing results obtained by laboratory methods with those obtained by the blood pressure age procedure using data given in the original papers (for example the reporting of a single blood pressure determination in some studies without assurance that this was a stable level) the study was considered sufficiently rigorous to indicate whether the blood pressure age method is essentially valid

Results with the older methods of determining cardiac output—acetylene nitrous oxide and ethyl iodide—compared remarkably well with those of the blood pressure age procedure The Fick and dye methods gave higher values but with virtually all the procedures studied the blood pressure age formulas yielded estimations which were highly comparable The validity of the comparison was found to hold for patients with anemia during exercise during anoxemia after hemorrhage after injection of epinephrine and in thyrotoxicosis

Determination of cardiac output by formulas relating blood pressure and age is innocuous and practicable Duplicate determinations in resting subjects agree closely Starr considers the intricacies and hazards and perhaps inherent errors of the more complicated methods recommendations for use of simpler blood pressure age formulas

Effects of Congestive Heart Failure on Blood Volume as Determined by Radiochromium Tagged Red Cells were studied by Seymour Eisenberg[1] (Southwest Med School) in 26 patients Heart failure was classified as mild moderate or severe according to duration severity and tractability of the congestive process

Blood volume red cell mass and plasma volume exceeded the values for normal subjects by 22% 25% and 17% In

(9) C lat on 9 664-681 M y 1954
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Solutions of differing concentrations of these ions were sub stituted for drinking water Serum and muscle analyses were done in each experiment Loads of sodium bicarbonate did not produce hypochloremic alkalosis as long as potassium chloride intake exceeded 0 5 mM/kg /day even though sodium bicarbonate intake was 10 30 mM/kg /day It was not possible to produce alkalosis in this way in the absence of potassium deficiency as demonstrated by muscle analy sis When hypochloremic alkalosis occurred as a result of potassium chloride restriction muscle analysis demonstrated low muscle potassium and high intracellular sodium

In a second experiment sodium bicarbonate 15 mM/kg was injected intraperitoneally into normal and potassium deficient rats (made so by diet and prior administration of desoxycorticosterone acetate) During the 12 hours after loading normal animals excreted 10 mEq sodium and 5 mEq potassium/kg essentially no chloride was excreted Alkalosis did not occur Potassium deficient animals how ever excreted only 6 mEq sodium/kg and no potassium almost 1 mEq chloride/kg was excreted Severe hypochlo remic alkalosis was present 12 hours after loading

Rats previously made hypochloremic and alkalotic were given injections of potassium bicarbonate, 3 mM/kg twice daily After 24 mM/kg had been given serum bicarbonate and chloride concentrations were normal This correction was associated with excretion of citrate in the urine little increase in bicarbonate excretion and essentially no change in urinary acidity Thus it appears that citrate may spare chloride in renal defense Potassium appears to be essential for maximal conservation of chloride in this manner

The experiments suggest that potassium deficiency may alter the ratio of sodium and chloride in the tubular reab sorbate affecting both concentrations and volume of extra cellular fluid

[This work would appear to have an important direct bearing on the treatment of congestive heart failure Patients with this disorder tend to develop potassium depletion This is only in part the result of the fre quent and at times injudicious use of mercurial diuretics The anorexia of congestive heart failure often leads to inadequate potassium intake It is likely that adrenal steroids are also concerned in this mechan m Potassium salts should be administered routinely to all patients with congestive heart failure who have a reasonably normal urine volume who do not have grave renal impairment and who are receiving frequent doses of mercurial diuretics This is especially important when the patient has prolonged periods of anorexia In the presence of mar of

kidney function or of marked oliguria, such salts should be administered only with the greatest caution —Ed]

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(1) Ibid 10 90 911 J m 1954

patients with severe heart failure blood volume values exceeded those of the normal group by 38% values of the mild group exceeded those of the normal group by only 14% The magnitude of the hypervolemia was correlated with the degree of cardiac enlargement but not with the increase in venous pressure cause of the heart disease or quantity of edema fluid The circulating red cell mass was consistently expanded during the congestive state selective expanison of the plasma volume was not encountered

Following treatment blood volume decreased significantly in 50% shrinkage in blood volume occurred only in subjects whose heart size decreased with treatment The quantity of edema fluid was not correlated with the expansion of plasma volume before treatment or the decrease in plasma volume after treatment

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ELECTROCARDIOGRAPHY AND ARRHYTHMIAS

Activation of Interventricular Septum Using multichannel recording apparatus and procedures Allen M Scher Allan C Young Arthur L Malmgren and Robert V Erickson examined the electric invasion of the interventricular septum Multipolar electrodes were inserted perpendicularly into the septum through the right wall and cavity with success in 25 dogs 3 monkeys and 1 goat

The records indicated that the earliest activity in the interventricular septum is usually on the left near the first branching of the left conducting bundle From this point activity spreads over the left septal surface at about 1 m/second and through the muscle wall at about 0 3 m/second About 5 msec later similar activity commences on the right near the base of the anterior papillary muscle where the right bundle first branches Most of the septum is excited by double envelopment from both endocardial surfaces with a slight preponderance of spread from the left

The fast conducting system conforms in its distribution to the Purkinje tissue On stimulation it conducts at a velocity of about 1 m/second but does not extend into the center of the septum Conduction through the center of the

(2) Circulation R s 3 56-64 January 1955

septum is syncytial in character There are no connective tissue or other barriers to conduction

A septal contribution to the ECG is probably most evident early in ventricular invasion when only the septum is active This activity seems to correlate well with the Q wave in lead II The septal contribution to the later portions of the QRS is probably minimal due to (1) the opposite direction of the two main septal vectors (2) the overriding of septal activity by activity in the wall and (3) the fact that the entire septum is usually excited in 25 msec

Studies on Mechanism of Ventricular Activity—*XII Early changes in RS T segment and QRS complex following acute coronary artery occlusion Experimental study and clinical applications*—Using slender intramural electrodes Louis Rakita Jean Louis Borduas Sol Rothman and Myron Prinzmetal[3] (Los Angeles) studied the electric effects in dogs ventricles injured by coronary artery ligation Electrodes were plunged into the ventricle for measurable distances and epicardial leads taken with cotton tipped electrodes After the current of injury following this manipulation had subsided a suture was tightened around the left anterior descending coronary artery Discoloration of an epicardial area followed with loss of contractility as demonstrated by outward ballooning during systole Electrodes were variously located in the area of discoloration areas immediately adjacent and occasionally on the posterior surface of the heart

Control studies before coronary artery ligation showed epicardial R waves followed by S waves and isoelectric or slightly elevated S T segments T waves were usually inverted Intramural subepicardial leads showed smaller R waves and larger S waves As the distance from the epicardium increased the initial R wave in the intramural leads diminished rapidly in width and amplitude and was imperceptible at midventricular levels The inner third of the ventricular wall and cavity leads showed pure QS waves

After coronary artery ligation epicardial leads from the discolored areas showed S T segment elevation with maximal elevation at the center of the injured area and a decrease as the periphery was approached Electrodes just outside the sharply demarcated area showed isoelectric S T

(3) Am H rt J 48 351 372 S pt mb 1954

segments Intramural and cavity leads recorded directly beneath the injured area showed S T segment elevation the amplitude diminishing along the axis from epicardium to cavity

After coronary artery ligation, the RS waves of the epicardium and outer ventricular layers and QS waves of the inner ventricular wall and cavity exhibited a change There was a gradual decrease in depth of the S or QS wave while the upstroke of the R became progressively taller, th e changes like the S T segment changes decreased in mag nitude from epicardium to cavity Subendocardial and mid mural leads recorded directly beneath normal appearing epi cardium adjacent to the injured epicardial area showed ele vated S T segments whereas the overlying epicardium showed i oelectric S T segments This and other evidence indicate that injuries produced by coronary artery liga tion are broader intramurally than at the epicardium

In no instance were depressed S T segments recorded from uninjured epicardium or intramural muscle adjacent to the injured region nor did they occur in cavity leads or in subendocardial leads recorded within 0 5 mm of the cavity directly beneath injured epicardial areas

The evidence obtained indicated that the injured region was more positive from endocardium to epicardium, but wider from epicardium to endocardium Ve tors reflecting electric activity of this area will therefore be more positive the more centrally situated they are over the injured area whereas at a large angle from the center of the injured area the vector will reflect less of the demonstrated positiv ity of the injured muscle S T segment depression was shown to occur with the well recognized method of placing an electrode opposite an area of S T segment elevation and as a result of unknown functional changes at the myocardial surface Evidence indicated that the depression is not oc casioned by subendocardial ischemia as has been generally supposed

[The work of the Prinzme al group is revolutionary in the electrocardiographic field. Particularly important is their observation tha large portions of the myocardium are es entially silent in the electrocardiographic sense Likewise important is their observation that minor physiologic variance such as changes in temperature and in pressure may produce marked electrocardiographic changes Their work furnished a firm foundation for the clinical observation of the la rallelism

between the gravity of the clinical state and the degree of abnormality of the electrocard ogram.—Ed]

XIV Clinical and experimental studies of accelerated auriculo entricular conduction—Borduas Rakita Kexford Kennamer and Prinzmetal[4] report seven clinical cases with ECG patterns characterized by a short P R interval of con stant or varying duration The QRS complex was either normal or aberrant The abnormality can occur in normal subjects or may be a result of organic heart disease Nodal rhythm and partial heart block occurred in some cases they are not of the classic Wolff Parkinson White syndrome

In 40 dogs cocaine formaldehyde or acetylstrophanthidin was injected in the A V node In 11 exactly the same va riety of P R and QRS abnormality seen in the seven clinical cases developed Heart block and nodal rhythm occurred in the other animals In 10 control injections in other parts of the heart did not produce any of these ECG phe nomena

The normal function of the A V node is to delay passage of the impulse from auricle to ventricle This delay ac counts for the major portion of the normal P R interval The injections pos ibly interfered with this function allow ing acceleration of conduction from auricle to ventricle with resultant shortening of the P R interval The ab normality has been termed accelerated conduction Since the ECG s in patients and dogs were identical the abnormality in the patients also may have been due to disturbance of the A V node

There is evidence that the A V node is a sort of central nervous system of the heart and that from a physiologic viewpoint certain parts of the node supply specific parts of the ventricle In cases of short P R intervals if the entire A V node is discharged prematurely the QRS is narrow and normal if only a part of the node is discharged the QRS is wide and aberrant

Two major theories of the short P R interval phenome non are (1) anomalous anatomic pathways and (2) accel erated conduction through the normal pathway Complete heart block can be produced by a small lesion in the A V node in man and animals It seems unlikely that the aber rant anatomic pathways can have a physiologic function

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(4) Ci lat on 11 69 88 J ry 1955

since they do not function after the A V node is destroyed In this study complete heart block eliminated all the accelerated conduction through the normal pathway Completing the second theory

[This investigation and the previous studies of the Prinzmetal group on the same general subject appear to have furnished definitive refutation to the concept that the Wolff Parkinson White electrocardiographic abnormality is the result of conduction through an aberrant bundle It should be emphasized that the presence of these various types of accelerated conduction does not in itself furnish information concerning the presence or absence of cardiac disease Patients with such abnormalities may or may not have structural disorders of the heart and may or may not be subject to ectopic tachycardia The decision like almost all others pertaining to the heart must rest on the clinical rather than on the electrocardiographic findings Too often these patients are considered to have bundle branch block and grave structural heart disease We need to be constantly reminded that treatment should be directed at the patient and not at the electrocardiogram —Ed]

Three Main Vectors of Ventricular Activation Process in Normal Human Heart I Its Significance Dante Peñaloza and Joao Tranchesi[5] (Inst Nacional de Cardiologia de Mexico Mexico City) report a study of the ventricular activation process (V A P) at the body surface of 25 normal males aged 20-40 carried out by means of multiple simultaneous ECG leads To reduce the discrepancies between real and calculated vectors vector analysis was facilitated by means of a plastic model in which the form of the thoracic cage as well as the location of the apparent electric center (site of null potential) was particularly considered

Three main instantaneous vectors correspond to the V A P The first vector 1 or septal vector always orients forward as a rule to the right and represents early septal electric forces Vector 2i or left ventricular vector points to the left down and back toward the free left ventricular wall and corresponds to the predominant electric activity originated in this ventricle Vector 3 or basal vector usually goes back to the right and up representing the depolarization of basal regions of the ventricular mass including the septum

These vectors are inscribed on the average at 0 01 0 04 and 0 064 second respectively after onset of the QRS complex Determination of the three vectors from the scalar curve permits one to follow the spatial sequence of the

(5) Am. Heart J 49 51-67 Jan ary 1955

V A P and one to infer potential variations at different points of the body surface

QRS Complex Deformity of Myocardial Infarction in the Human Subject was studied by Robert P Grant and Raymond H Murray[6] (Nat l Inst of Health) by two approaches In the first vector methods were used to compare the distribution of electric positivity and negativity on the chest surface for several instants during the QRS cycle in 38 normal subjects with that in 77 subjects with QRS complex deformity of myocardial infarction In the second approach pre and postinfarction tracings were compared by vector methods in 187 subjects as a controlled study of the QRS complex defect produced by infarction

In every subject there is a region of the chest where Q waves of 0 04 second s duration can be recorded The only difference between the Q area of the normal subject and that of the subject with myocardial infarction is in its location

The easiest and most rational way to decide whether a Q wave of 0 03-0 04 second s duration in a given lead is normal or abnormal is to study the distribution of the Q area for that subject In most cases this can be done from the conventional clinical tracing by plotting null contours for two or three instants during the first 0 04 second of the QRS interval If this is difficult or inconclusive V leads may be recorded in a systematic manner from the chest surface and the Q area plotted from the deflections

In 95% of infarctions in which QRS deformity is produced at least the first 0 04 second of the QRS interval is deformed This means that from a pattern point of view a Q wave should be at least 0 04 second in duration in a given lead before it can be considered diagnostic of myocardial infarction

Four types of deformity of the terminal part of the QRS complex without prolongation of the QRS interval were encountered in association with myocardial infarction Two of these were considered to be types of peri infarction block They were seen in about a third of the cases

Whatever the actual anatomic location of the infarct it must have an electric effect on the septum or paraseptal regions of the heart and must also involve the first part of the heart to undergo depolarization in order to produce

(6) Am J Med 17 587-609 N embe 1954

QRS complex deformities of a type currently considered diagnostic of infarction This represents only a part of the entire left ventricle and perhaps helps explain why only a limited number of infarctions proved at autopsy are recognized electrocardiographically

Vectorcardiographic Diagnosis of Myocardial Infarction Louis Wolff[7] (Harvard Med School) reports a comparative study of vectorcardiographic and electrocardiographic interpretation with pathologic correlation in 50 consecutive cases which came to autopsy among which were 22 (exclusive of those with left bundle branch block) with myocardial infarction

The cardiac vector is analyzed in relation to three natural co ordinate axes of the body by projection on three mutually perpendicular planes horizontal sagittal and frontal Except in instances of unusual heart position displacement of electric forces in the anteroposterior axis occurs in anterior and high posterior wall lesions in the transverse axis in lateral wall and septal lesions and in the vertical axis in lesions involving the inferior or basal portion of the posterior wall of the left ventricle The abnormal vectors are oriented posteriorly and down in anterior infarction anteriorly and down in high posterior infarction up and posteriorly in inferoposterior wall lesions to the left in lesions close to the interventricular septum and to the right in lateral wall involvement Clockwise inscription of the posteriorly placed horizontal projection indicates anterior infarction and clockwise inscription of the horizontally placed frontal loop is diagnostic of posterior wall infarction

Acute infarction is characterized by an open QRS loop and long narrow T loops In healing or old infarction the QRS loop tends to close and the T loop is small and round An open QRSsE loop corresponds to S T segment deviation in the ECG The end of the loop in relation to the 0 point is to the right anterior and up in acute anterior myocardial infarction right posterior and down in posterior myocardial infarction left anterior and down in acute fibrinous pericarditis right and up with minimal or no anteroposterior deviation in left ventricular hypertrophy and left posterior and up in right ventricular hypertrophy

(7) Dis Chest 27 63 281 March 1955

Comparison of vectorcardiographic and ECG interpretations indicates the definite superiority of vectorcardiograms in disclosing myocardial infarction and right and left ventricular hypertrophy singly and combined (especially striking when hypertrophy and infarction coexist) High posterior and some anterior lesions multiple infarcts and septal lesions are all more easily diagnosed by vectorcardiogram

Misinterpretation of Electrocardiograms with Postprandial T Wave Inversion Isidore Rochlin and W L Jack Edwards[8] (Med College of Alabama) report four cases in which coronary artery disease was diagnosed largely on the basis of occasional flattening or inversion of T waves in the bipolar or lateral V leads (V_4 V_5 V_6) Coexisting chest pain supposedly anginal was present in two and was shown to be of noncardiac origin It was found that the ECG changes could be induced at will by a high carbohydrate meal and prevented by simultaneous administration of potassium chloride with the meal Exercise did not lower the T waves in the same leads

It is known that after a meal T waves tend to become lower This may be due to a sympathetic effect which decreases plasma potassium Another explanation is that plasma potassium decreases due to entrance of food into the gastrointestinal tract which stimulates insulin secretion The insulin in turn stimulates the liver and skeletal muscle to deposit potassium with glycogen It is known that 100 Gm of glucose orally lowers plasma potassium in a similar fashion

Normal subjects and those with arteriosclerotic heart disease showed the same ECG response to high carbohydrate meals the effect of which could be prevented by the addition of 3 Gm potassium chloride to the meal Despite definite trends of T wave lowering no consistent changes were detected in spatial vector angles or in ventricular gradients

Nondiagnostic Electrocardiographic Patterns often accompany reversible disease Nathaniel E Reich[9] (State Univ of New York Brooklyn) presents the commoner ECG features of such conditions In neurocirculatory asthenia variations are due to heart position and the effects of exer

(8) C 1 t on 10 843 849 Decembe 1954
(9) D Chest 25 516-5 8 M y 1954

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cise body position and hyperventilation Inversion of the T wave in lead II or even in lead III may be noted and is usually caused by altered heart position S T and T wave changes may occur during hyperventilation and are probably due to the induced alkalosis Systemic infections often cause a nonspecific myocarditis any of the following changes may be present increased P R interval arrhythmias, inverted T waves S T segment changes low amplitude and slurring of the QRS complexes and bundle branch block A constantly changing ECG is the most diagnostic of all findings

The ECG manifestations of acute nonspecific pericarditis are chiefly due to subepicardial myocarditis and include elevation of the RS T segments with dome shaped or peaked T waves and reversion to normal within a few weeks There is no depression of the RS T segment at any time no classic reciprocal T wave deflections in leads I and III and no Q pattern the RT elevations are usually less marked and of much longer duration than in acute infarction In chronic constrictive pericarditis, the ECG shows low or inverted waves QRS complexes of low voltage in standard leads auricular fibrillation late in the disease and fixation of the electrical axis

Cardiac involvement in thyrotoxicosis is variable hence ECG tracings are not always helpful Arrhythmias may be present there may be low or inverted T waves especially in lead II and more rarely tall rounded or pointed T waves A left ventricular strain pattern becomes evident in long standing cases The ECG of most untreated patients with myxedema shows sinus bradycardia low voltage QRS complexes and absence or inversion of T waves in standard or chest leads There may be varying degrees of auriculo ventricular block In beriberi heart disease bradycardia low voltage QRS complexes inverted T waves and prolonged Q T intervals are common The changes found in hyperpotassemia include early elevation and peaking of the T waves increased P R interval and perhaps auricular standstill obliteration of the S T segment with the T wave originating from the S wave and late widening of the QRS complex and a biphasic ventricular complex By contrast in hypopotassemia there are prolonged Q T and P R intervals flat or inverted T waves depressed S T segments de

creased QRS amplitude intraventricular block and occasional prominent U waves With hypercalcemia there is shortening of the Q T interval at the expense of the S T segment prolongation of the P R intervals and slurred QRS complexes are inconstant In hypocalcemic conditions there is prolongation of the Q T interval This differs from that found in hypopotassemia which ensues as a result of rounding and broadening of the T wave

[Year by year there appears to be a steady increase in the number of patients who have good hearts and bad electrocardiograms The widespread unfortunate tendency to base prognosis and treatment on minor electrocardiographic changes is leading to a large increase in the number of psychic invalids This point of view which was expressed by the late Frank N Wilson some years ago needs increasing emphasis now

Another fairly common cause of unimportant T wave changes is contusion of the heart It appears to be common in boxers as well as in individuals who have experienced steering wheel injuries in automobile accidents —Ed.]

Elevation of RS T Segment Apparent or Real in Right Precordial Leads as Probable Normal Variant In 10 selected patients with no collateral evidences of heart disease Joseph Edeiken[1] (Univ of Pennsylvania) found this deviation in one or more of the right precordial leads although the left precordial leads were normal Characteristically the apparent RS T segment arose from an R wave was most elevated at its origin then sloped gradually down to resemble the latter half of a T wave No significant abnormality was found in standard or unipolar limb leads In four there was slight elevation of the RS T segment in aV_L and in one a slight depression of RS TaV_R

Although the pattern suggested localized myocardial injury none was found In four patients the pattern had persisted over five years Available evidence strongly suggests that this finding does not necessarily indicate myocardial disease

Peculiarities of the African s Electrocardiogram and Changes Observed in Serial Studies are described by H Grusin[2] (Univ of Witwatersrand) It was found that 63% of 159 consecutive medical patients and 22% of healthy nurses had ECG s which deviated from the accepted normal The following patterns were evident

1 S T segment depression and inverted T waves were found in the precordial leads in a third of the patients and

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(1) *Am Heart J 48 331 339 Septembe 1954*
(2) Circulation 9 860 867 J 1954

cise body position and hyperventilation Inversion of the T wave in lead II or even in lead III may be noted and is usually caused by altered heart position S T and T wave changes may occur during hyperventilation and are probably due to the induced alkalosis Systemic infections often cause a nonspecific myocarditis any of the following changes may be present increased P R interval arrhythmias inverted T waves S T segment changes low amplitude and slurring of the QRS complexes and bundle branch block A constantly changing ECG is the most diagnostic of all findings

The ECG manifestations of acute nonspecific pericarditis are chiefly due to subepicardial myocarditis and include elevation of the RS T segments with dome shaped or peaked T waves and reversion to normal within a few weeks There is no depression of the RS T segment at any time no classic reciprocal T wave deflections in leads I and III and no Q pattern the RT elevations are usually less marked and of much longer duration than in acute infarction In chronic constrictive pericarditis the ECG shows low or inverted waves QRS complexes of low voltage in standard leads auricular fibrillation late in the disease and fixation of the electrical axis

Cardiac involvement in thyrotoxicosis is variable hence ECG tracings are not always helpful Arrhythmias may be present there may be low or inverted T waves especially in lead II and more rarely tall rounded or pointed T waves A left ventricular strain pattern becomes evident in long standing ca es The ECG of most untreated patients with myxedema shows sinus bradycardia low voltage QRS complexes and absence or inversion of T waves in standard or chest leads There may be varying degrees of auriculo ventricular block In beriberi heart disease bradycardia low voltage QRS complexes inverted T waves and prolonged Q T intervals are common The changes found in hyperpotassemia include early elevation and peaking of the T waves increased P R interval and perhaps auricular standstill obliteration of the S T segment with the T wave originating from the S wave and late widening of the QRS complex and a biphasic ventricular complex By contrast in hypopotassemia there are prolonged Q T and P R intervals flat or inverted T waves depressed S T segments de

(2) Typical changes in T wave associated with relatively minor change in QRS complexes (20 cases) (3) Tall R waves in leads V_5 and V_6 commonly seen in left ventricular hypertrophy (left strain variants) (13 cases) (4) Typical changes in T waves and QRS complexes suggesting presence of right ventricular hypertrophy or partial or complete right bundle branch block (six cases) (5) Inversion of T wave in lead V_3 less than 5 mm (nine cases)

Of 62 patients with only the typical change in T wave 38 (61%) had clinical evidence of myocardial infarction or severe coronary insufficiency One had chronic constrictive pericarditis and had had surgical exploration of pericardium and heart In 23 coronary insufficiency or myocardial infarction could not be definitely established but could not be excluded In 21 of the group later ECG s showed a reversal in direction of T waves to an upright position All but 2 of 20 patients with typical T wave changes and minor QRS changes had clinical evidence of myocardial scarring or severe coronary insufficiency None of the 13 with ECG s of left strain variant type presented substantial clinical evidence of myocardial infarction or severe coronary insufficiency but about half of these and of those with shallow T wave inversions had angina pectoris

Autopsy on 4 of the 62 in the typical ECG category and on 5 others showed healed subendocardial infarction in 8 Infarcted regions were predominantly in the lateral wall of the left ventricle in four in the anterior wall in three and at the basal portion of the posterior wall in one In the ninth case scattered lesions of healed infarction were identified microscopically but no gross scarring was evident

Expressed in term of the dipole theory deeply inverted T waves are commonly an expression of the presence of a transmurally disposed region of myocardial ischemia under which there may be a subendocardial zone of myocardial infarction

Basic ECG (Night ECG) Its Recognition and Diagnostic Significance Diurnal variations in ECG which affect the PQ interval S T segment and height of the T waves have long been known Schellong found rhythmic changes in early as well as in healing myocarditis and in neurocirculatory asthenia These changes were thought to depend on the

14% of the nurses These changes were also apparent in the limb leads if they were present in all precordial leads Typically the end deflection consisted in a deeply inverted T a depression of J and an S T segment bowed upward to form a wide shoulder In 17 patients these were most evident in the right ventricular leads Within a few weeks the inversion became shallower and the T wave took on a cove plane appearance caused by a high curved S T segment Subsequently the rather labile T waves remained inverted to varying depths or became upright The changes were found to be cyclic in some cases

2 S T segment elevation and tall T waves in the precordial leads were found in a fourth of the patients and in two nurses In a typical left ventricular lead the terminal deflection showed elevation of the S T segment and a tall bold T wave with a slowly rising ascending limb and a sharply falling distal limb ending in a U wave Some subjects showed tall R waves unrelated to the degree of S T elevation or the height of the T waves Follow up examinations showed wide variability in S T elevation shape of T waves and height of R waves Inhalation of amyl nitrite usually reduced the S T elevation and the height of the T wave

3 Rounded or flat T waves in the precordial leads were occasionally found Combinations of the first two patterns were also seen in a few patients

The ECG peculiarities were apparently not due to heart disease Postmortem examination of two patients showed no cardiac abnormalities No correlation was found between the ECG patterns and heart position or body size The author considers that the unusual patterns are comparable with the precordial T wave inversions found in children Undernutrition may play a part in these ECG changes

Certain Clinical States and Pathologic Changes Associated with Deeply Inverted T Waves in Precordial Electrocardiogram were determined by correlation of clinical and ECG findings in 110 cases by Raymond D Pruitt Clayton H Klakeg and Lemuel E Chapin[3] (Mayo Clinic and Found) ECG s were classified in five groups (1) Typical T deflection in lead V_3 inverted to at least 5 mm and as deeply inverted as the T wave in lead V_6 or more (62 cases)

(3) Circulation 11 517 530 Ap 1, 1955

or conduction In either case however the A V node is by passed and A V conduction time abbreviated Ventricular *depolarization begins via the anomalous route* and appears to proceed from epicardium to endocardium This so distorts the QRS complex that it hides the configuration of myocardial infarction if present Clinically the most common feature is the paroxysmal tachycardia found in over 70% These individuals do not have a higher incidence of cardiovascular diseases or of other ailments Pregnancy and childbirth are not influenced nor is the syndrome a contraindication to surgery These people are able to lead normal lives with symptoms present only during episodes of *tachycardia However sudden* death has been reported and life insurance experience indicates that candidates with the syndrome are substandard risks

Diagnosis of the syndrome depends on the ECG features It is important to recognize that ECG representations of other heart disease myocardial infarction and bundle branch block in particular may be obscured by the abnormal QRS but can be demonstrated by suppression *of the anomalous* mechanism with such drugs as atropine quinidine amyl nitrite inhalation procaine amide deep inspiration or combinations of these procedures

P Wave in Electrocardiogram in Diagnosis of Heart Disease has perhaps been overlooked Paul Thomas and David Dejong[6] (London Hosp) review the significance of this deflection in 100 normal subjects and 245 with heart disease All had normal rhythm rate and conduction Four major types of wave were found bifid diphasic pointed and convex *The bifid waves were subdivided into those with* a higher first peak those of the second peak type and those with peaks of equal height Blunted or impure bifid waves producing slanting downstroke flat topped or slanting upstroke were less common Diphasic P waves were considered to resemble the true intrinsic deflection seen with direct recordings of auricular activity A pointed wave with a single point at the apex and *no negative component* represented activity of one atrium These derivations follow previous demonstration of the appearance of direct auricular records It has also been shown that the first component of the P wave is derived from right atrial activity and

(6) Brit Heart J 16 241 254 July 1954

autonomic nervous system and to carry a good prognosis

G Damm F Hammer and W Pretzsch[4] (Goppingen Germany) recorded morning and evening (between 10 and 12 p m) ECG s of 53 patients with neurocirculatory asthenia and of 5 with mild postinfection myocarditis Most complained of palpitation and feeling of pressure and tightness in the chest They often had labile blood pressure moist hands hyperhidrosis and increased dermographism The late hours for the ECG were chosen to study the diurnal variations to take advantage of the patient s emotional and physical rest and to exclude the effects of eating

Whereas the morning ECG of these patients revealed S T depression and a flat or isoelectric T wave in many the night or rest ECG was normal in 34 patients and much improved in 13 In eight the same changes appeared at night and in three the S T depression increased and the T waves became flatter There was no relation between pulse rate and S T changes The large number of ECG s which returned to normal by night indicates the influence of the autonomic nervous system on ECG changes

Syndrome of Short P R Interval with Abnormal QRS Complexes and Paroxysmal Tachycardia (Wolff Parkinson White Syndrome) Louis Wolff[5] (Harvard Med School) points out that distinctive features of this syndrome are the unusual ECG and paroxysmal tachycardia The P R interval is 0 1 second or less in about 85% of patients The QRS complex is 0 11 or 0 12 second in almost half the cases but may be as long as 0 2 second or occasionally in normal limits However it is characteristically slurred heavily in the initial deflection and may be notched QS deflections may be seen in leads II III aV_f superior esophageal and right sided precordial leads Q waves do not occur in the left sided precordial tracings A noteworthy feature is the occasional spontaneous or induced transformation in the ECG The paroxysmal tachycardia is always supraventricular generally resembling auricular tachycardia but occasionally is similar to paroxysmal auricular fibrillation or flutter

The disorder is probably congenital but the mechanism is unclear It may be due to anomalous impulse formation

(4) D utsch m d Wchn h 80 41-44 Ja 7 1955
(5) C culat on 10 282 291 A gust 1954

right ventricular hypertrophy with systolic overloading of the right ventricle—tall R wave in V_1 and V QRS complex of the rR Rs R and qR type (2) left ventricular hypertrophy with or without diastolic overloading of the left ventricle in V_5 and V_6—tall or normal R wave when a small deflection was expected due to accentuated right ventricular hypertrophy deep Q wave delayed intrinsicoid deflection positive T wave frequent complexes of qRs or qRS type with a positive T wave

Three degrees of patent ductus arteriosus can be differentiated In patent ductus arteriosus without pulmonary hypertension left ventricular diastolic overloading is shown High peaked symmetrical T waves are seen in the left precordial leads with signs of left ventricular hypertrophy the QRS complex in V_1 is normal In patent ductus arteriosus with moderate hypertension ECG evidence of right ventricular systolic overloading with right ventricular hypertrophy is observed in V_1 as well as signs of left ventricular overloading When pulmonary hypertension reaches values similar to those of the systemic circulation or higher signs of right ventricular systolic overloading with right ventricular hypertrophy increase and signs of left ventricular hypertrophy are masked

In some congenital heart conditions with cyanosis such as in the tetralogy of Fallot tricuspid atresia and transposition of the large vessels a tall peaked widened and notched P wave referred to as congenital P has been described in leads I and II or II and III Such P wave changes are determined by dilatation or hypertrophy of the right atrium position of the heart low oxygen saturation in the arterial blood and a systolic overloading of the right ventricle

The ECG of pure pulmonary stenosis may vary from normal or slight changes to tracings showing maximal right ventricular hypertrophy of the systolic overloading type These variations depend on the systolic hypertension of the right ventricle and degree of pulmonary stenosis and right ventricular hypertrophy

From the ECG point of view the picture in the trilogy of Fallot is similar to that of pure pulmonary stenosis Cases of tetralogy and pentalogy of Fallot behave as pure pulmonary stenosis or as a trilogy with a moderate systolic hypertension of the right ventricle

the second part from left atrial activity in both health and disease Bifid waves were especially evaluated as in this asynchronous recording of auricular activity the contribution of each auricle could be examined

In healthy subjects a bifid wave was present in one or more leads in 92% of the ECG s taken appearing most commonly in CR_4 The first peak type was common in CR_1 but never occurred in CR_7 second peak types were found frequently in CR_4 and CR not in CR_1 No P wave was more than 3 0 mm high 0 10 second in duration or, when bifid with more than 0 04 second between peaks

ECG s of the 215 subjects with heart disease were then compared with normal record with recognition of the type and severity of the heart disease Right atrial abnormality is considered present when the P wave in CR_1 is tall (more than 2 5 mm) and is diphasic pointed or bifid of the first peak type Left atrial abnormality is present when a tall (more than 3 0 mm) bifid P wave of the second peak type occurs in CR_4 or CR_7 or an abnormally long peak interval (distance between peaks) occurs in a bifid wave in any lead regardless of voltage Combined atrial abnormality is suggested when a P wave deformity characteristic of both right and left atrial defect is present

Importance of Electrocardiographic Patterns in Congenital Heart Disease Demetrio Sodi Pallares and Federico Marsico[7] call attention to the value of ECG study in the diagnosis of congenital heart disease as shown by recent research at the Instituto Nacional de Cardiologia Mexico City Many tracings disclose hemodynamic alterations more accurately than clinical and radiographic findings

A high incidence of right bundle branch block has been found in atrial septal defect The auricular complex was definitely abnormal in 40% of 50 recently reported cases Peaked P waves with increased duration (0 12 second or more) and greater voltage suggested enlargement of both atria The morphology was a combination of a mitral P plus congenital P First degree atrioventricular block was found in 26% of the cases Incomplete (80%) or complete (6%) right bundle branch block was the most frequent finding in the ventricular complex

The ECG signs of ventricular septal defect are (1)

(7) Am H art J 49 0 17 Feb ary 1955

depression of the S T segment and widening of the QRS complex.

Clinical and Electrocardiographic Differentiation of Supraventricular and Ventricular Tachycardias with Regular Rhythm was investigated by V Schrire and L Vogelpoel[9] (Univ of Cape Town) in 79 patients Only those whose clinical findings could be confirmed by simultaneous sound and by jugular venous and ECG tracings were included

In 24 of 28 patients with supraventricular tachycardia auscultation revealed single or normally split first and second heart sounds In most sound tracings revealed single or broad first sounds and the width of splitting was 0 02 0 04 second The ECG in all of these showed a QRS interval of normal duration In the four others there was wide splitting of the first (average 0 06 second) and the second heart sounds and bundle branch block was present None of the patients with regular rhythm had alteration in intensity of the first sound The ECG counterpart was a constant P R interval in each case In 26 the jugular venous pulse was normal and irregular independent Cannon A waves were not apparent The rapid small *a* waves of auricular flutter were seldom recognized clinically In the remaining two nodal tachycardia and 1 1 auricular flutter regular Cannon A waves occurring at the same rate as the pulse were striking clinical features In only two instances were esophageal leads needed to demonstrate auricular activity Standard leads showed satisfactory P waves preceding each ventricular complex in the others

In 10 patients with ventricular tachycardia wide splitting of the first and second heart sounds was present The time interval between onset of the major high frequency components of the split first sound averaged 0 08 second range 0 05-0 10 second The ECG always showed an abnormally wide QRS complex the ectopic focus arising from the left ventricle in eight Changing intensity of the first heart sound was noted in eight indicating auriculoventricular dissociation the intensity of first sound remained constant in the other two When there was varying intensity of the first heart sound the jugular venous pulsations had irregular independent Cannon A waves which were absent

(9) Am. Heart J 49 16 187 February 1955

The most characteristic ECG signs of Ebstein s disease are incomplete or complete right bundle branch block and paroxysmal ventricular premature beats A peaked P wave with an increased duration in lead II and lead III may also be found Intra atrial recordings above the tri cuspid valve may aid in diagnosing Ebstein s disease if a monophasic ventricular wave is recorded in the lower portion of the right atrium

Effects of Acute Removal of Potassium from Dogs Changes in Electrocardiogram are discussed by John M Weller Bernard Lown Rolf V Hoigne Norman F Wyatt Modestino Criscitiello John P Merrill and Samuel A Levine[8] (Harvard Med School)

Potassium was rapidly removed from the circulating blood of 14 dogs on 22 occasions by a Kolff type hemodialyzer The technic of dialysis was modified (1) A flow of 100 300 ml blood/minute through the machine was obtained by cannulation of the femoral artery and vein (2) Length of cellophane tubing was limited to 70 ft (3) Before dialysis the dead space in the machine was filled with 400 ml heparinized blood from donor dogs (4) The composition of bath fluid which approximated the electrolyte concentration of dog serum was altered only in respect to potassium The ECG s were taken during removal of potassium and following restoration of the serum level to its predialysis value

Potassium extraction occurred in a phase of rapid reduction (during the first hour) of serum level to half the initial value (to 2 mEq /L) followed by a phase of continued extraction of body potassium with the extracellular concentration remaining fixed Potassium extracted during this phase is presumably derived from the cellular compartment

ECG changes from potassium extraction can be classified in three groups (1) changes limited to the phase of rapid serum potassium decline which consisted of increases in amplitude of the P wave widening and rounding of the T wave and prolongation of the P R interval (2) changes taking place throughout the process of removal consisting of shifts in the QRS axis and acceleration of heart rate and (3) changes during the phase of continuing extraction of potassium when the serum level remains fixed consisting of

(8) Circulation 11 44 52 January 1955

ternates with tachycardia or fibrillation in the same patient

Control of Certain Cardiac Arrhythmias with Isopropyl Nor Epinephrine (IPN) is described by E E Schumacher Jr and C L Schmock (Henry Ford Hosp) Included among the 28 patients were some with Stokes Adams seizures on the basis of ventricular tachycardia

Certain consistent results were observed in all patients There was generally a rise of 10 20 mm Hg in systolic blood pressure and a similar drop in diastolic In complete auriculoventricular block the rate of the pacemaker always increased considerably and with one exception the pacemaker relocated in the vicinity of the auriculoventricular node When dissociation persisted both auricular and ventricular rates increased simultaneously although not always to the same degree In cases without complete heart block IPN exerted its primary effect on the sinus area although a definite action on the auriculoventricular node was also observed In no instance did IPN induce ventricular fibrillation or ventricular tachycardia although the latter was abruptly halted in two patients Some depression of the S T junction was noted in two cases but no definite changes were noted in the T waves Several patients had palpitation with 0 2 mg IPN subcutaneously but none experienced feelings of air hunger or substernal oppression One patient with ventricular tachycardia and the Stokes Adams syndrome and those with hyperactive carotid sinus syndromes have been maintained on sublingual IPN (20 mg every four to six hours) for three or four months with good results This agent would now appear to be the drug of choice in these conditions

Syndrome of Alternating Bradycardia and Tachycardia was observed by D S Short[3] in four patients two with mitral valve disease (one of them with left bundle branch block) one with aortic valve sclerosis and a fourth with no evidence of heart disease During bradycardia the sinus rate was generally 30 50/minute with sinus arrhythmia always present and a wandering pacemaker and periods of sinus standstill demonstrated in some During tachycardia the pacemaker was auricular varying between 180 and 200 /minute Auricular flutter was present in three patients

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( ) Am H rt J 48 933 940 Dec mbe 1954
(3) B t Heart J 16 08 14 April 1954

in the two patients in whom the first heart sound was constant In every case conventional leads showed wide QRS complexes and with two exceptions failed to demonstrate auricular activity It usually was impossible to differentiate ventricular tachycardia from supraventricular with bundle branch block The esophageal lead however demonstrated clear independent waves in 9 of 10 to establish the diagnosis

Adams Stokes Syndrome Treatment of Ventricular Asystole Ventricular Tachycardia and Ventricular Fibrillation Associated with Complete Heart Block Stanley R Robbin Samuel Goldfein Miles J Schwartz and Simon Dack[1] (Mount Sinai Hosp New York) report four cases of heart block with Stokes Adams syndrome to illustrate the two different mechanisms which may precipitate the attacks namely ventricular asystole and ventricular tachycardia or fibrillation Their cases and those of other workers indicate that treatment should be adjusted according to the underlying mechanism and to the individual patient

Epinephrine is the drug of choice for treatment of ventricular asystole but should be administered in sufficient dosage under ECG control It is contraindicated when ventricular tachycardia or fibrillation is the mechanism for the attacks Procaine amide and quinidine have been found to be ineffective and even harmful in ventricular tachycardia or fibrillation in the presence of heart block owing to their depressant effect on the junctional tissues

Isopropyl nor epinephrine (isuprel®) was given in two of the cases In one the causal mechanism was ventricular asystole and epinephrine invariably produced bursts of ventricular extrasystoles or short runs of ventricular tachycardia indicating myocardial irritability Isuprel® reduced the frequency of Adams Stokes attacks and terminated impending attacks when taken at onset of symptoms In the other case the causative mechanism was ventricular tachycardia and fibrillation Isuprel® therapy was followed by cessation of attacks This drug stimulates the higher ventricular centers and therefore does not predispose to ventricular fibrillation It appears the drug of choice when the basic mechanism for the Stokes Adams syndrome is ventricular tachycardia or fibrillation and when ventricular asystole al

(1) Am J Med 18 577 590 Ap 1 1955

hydrochloride and 8 a total dose of 10-40 mg /kg procaine amide hydrochloride All drugs were given at the rate of 5 mg /kg /minute until normal sinus rhythm returned or prohibitive toxicity developed

Vomiting occurred in all animals about five minutes after injection of ouabain later as the effects of the antiarrhythmic drugs wore off it recurred before the return of the ventricular tachycardia All drugs used restored sinus rhythm but dilantin® and procaine amide hydrochloride were superior in that no evidence of central stimulation followed their use whereas procaine hydrochloride and quinidine caused stimulation and convulsions in some animals Procaine hydrochloride was effective for a considerably shorter time than the other three and caused auricular tachycardia whereas the others caused restoration of normal sinus rhythm The only toxic symptom in the dilantin® group was transient nystagmus in one animal

Comparison of dosages of quinidine procaine amide and dilantin® used in this experiment with clinical usage shows a rather striking similarity Dilantin® used in amounts of 5 10 mg /kg clinically was effective in quantities of 10 30 mg /kg

Centrally Mediated Effects of Cardiac Drugs Strophanthin K Quinidine and Procaine Amide S J Weinberg and Thomas J Haley[5] (Univ of California Los Angeles) studied the extracardiac sites of action of varying doses of strophanthin K (0 02 0 55 mg) quinidine sulfate (5 50 mg) and procaine amide (50 100 mg) injected into the third cerebral ventricle of 25 trained unanesthetized dogs

Intraventricular injection of strophanthin K produced cardiac irregularities including bigeminy trigeminy bradycardia tachycardia ventricular extrasystoles and paroxysmal ventricular tachycardia Intravenous injection of equal or larger doses of this drug in the same or other dogs had little or no effect on the ECG

Intraventricular injection of quinidine sulfate produced paroxysmal auricular tachycardia nodal and ventricular extrasystoles and paroxysmal ventricular tachycardia Intravenous injection of equal or larger doses of the drug caused little or no ECG changes

The arrhythmic effect from intraventricular injection of strophanthin K was prevented or modified by prior intra

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with an auricular rate over 200 and with a 2 1 or a 4 1 block In these patients P' was inverted in leads II and III in the patient with auricular rate below 200 P was upright in leads I and II The paroxysms of tachycardia lasted from minutes to months two had attacks lasting a year The prominent symptoms were palpitation giddiness and sometimes unconsciousness The degree of disability in tachycardia was directly proportional to the ventricular rate Syncope often occurred with bradycardia and Stokes Adams attacks were the greatest hazard Large doses of atropine failed to raise the sinus rate to that achieved by a normal subject under similar conditions suggesting that hypervagotonia is not responsible for the bradycardia However, atropine intravenously did accelerate the auricular rate to normal resting levels

It is assumed that the cause is a state of subnormal activity of the sinoauricular node This is supported by observed episodes of auricular standstill following administration of quinidine or procaine amide The ideal drug for correction of the bradycardia would be one with atropine like properties and selective action on the cardiac branches of the vagus nerve The attacks of tachycardia were controlled safely with digitalis One patient had a total thyroidectomy and for unknown reasons had striking temporary symptomatic relief Another patient went spontaneously into auricular fibrillation and lost all symptoms of the syndrome A means of inducing auricular fibrillation would be of great value

Effect of Diphenylhydantoin Sodium (Dilantin®) Procaine Hydrochloride Procaine Amide Hydrochloride and Quinidine Hydrochloride on Ouabain Induced Ventricular Tachycardia in Unanesthetized Dogs is reported by Lois Mosey and Myra D Tyler[4] (Boston Univ) Dilantin® may be useful in treatment of digitalis induced ventricular arrhythmias Previous studies have demonstrated its effectiveness in abolition of ventricular tachycardia produced in dogs by ligation of the anterior descending coronary artery

METHOD—Ouabain 0 08 mg /kg was given to four groups of unanesthetized dogs Within an hour most dogs developed ventricular tachycardia some had to be given additional ouabain The control group then received 10% glucose in saline intravenously 12 received 10 30 mg /kg dilantin® 5 received 15 mg /kg procaine

(4) Circulat on 10 65 70 J ly 1954

hydrochloride and 8 a total dose of 10-40 mg/kg procaine amide hydrochloride All drugs were given at the rate of 5 mg/kg/minute until normal sinus rhythm returned or prohibitive toxicity developed

Vomiting occurred in all animals about five minutes after injection of ouabain later as the effects of the antiarrhythmic drugs wore off it recurred before the return of the ventricular tachycardia All drugs used restored sinus rhythm but dilantin® and procaine amide hydrochloride were superior in that no evidence of central stimulation followed their use whereas procaine hydrochloride and quinidine caused stimulation and convulsions in some animals Procaine hydrochloride was effective for a considerably shorter time than the other three and caused auricular tachycardia whereas the others caused restoration of normal sinus rhythm The only toxic symptom in the dilantin® group was transient nystagmus in one animal

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The arrhythmic effect from intraventricular injection of strophanthin K was prevented or modified by prior intra

(5) C rculat on Res 3 103 109 J ry 1955

ventricular injection of either quinidine sulfate or procaine amide The arrhythmic effects of intraventricular strophanthin K may be terminated or modified by intravenous quinidine sulfate procaine amide or sodium pentobarbital In travenous hexamethonium chloride can block these arrhythmias entirely by blocking sympathetic transmission at the ganglions

These results prove that cardiac irregularities observed after third ventricle injection of strophanthin K are centrally mediated The centrally induced cardiac effect of strophanthin K and quinidine sulfate are accompanied by autonomic manifestations resembling those seen in cases of clinical digitalis and quinidine toxicity

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CEREBRAL VASCULAR DISORDERS

Studies in Cerebrovascular Disease I Syndrome of Intermittent Insufficiency of Basilar Arterial System is described with 10 illustrative cases by *Clark H Millikan and Robert G Siekert*[6] (Mayo Clinic) The concept of the syndrome began to take form in study of the following case

Woman 67 in 39 days had 21 attacks of numbness and at times poor function of the left arm with dysarthria and dimness of vision in certain episodes Oxygen and CO_2 had no effect In some attacks the right side was involved The pattern of symptoms until the 3od day was definitely intermittent Evidence of brain damage was present from then on marking a shift from intermittent insufficiency of the basilar arterial system to arterial occlusion but intermittent attacks of numbness and poor use of the left arm continued Attacks stopped completely when anticoagulant action of tromexan® and dicumarol® became adequate (prothrombin time 35 45 seconds) She did well for about two months Fatal thrombosis of the basilar artery occurred when anticoagulant action was totally inadequate (prothrombin time 18 seconds) Autopsy revealed an old thrombus in posterior cerebral arteries with bilateral infarcts in the occipital lobes and a recent thrombus of the basilar artery extending into the right vertebral artery with infarction of the pons

Effects of impairment of the basilar arterial system vary depending on the site of involvement whether sudden or gradual complete or incomplete the adequacy of collateral circulation and cardiac output Symptoms include loss of vision double vision ptosis clouding of co snes con

(6) Proc Staff M t Mayo Cl 30 61 68 F b 23

fusion unconsciousness hemiparesis and hemiplegia dysarthria dysphagia sensory phenomena in the face one extremity or half of the body vertigo tinnitus vomiting unsteadiness and headache The same symptom on opposite sides of the body in definite attacks (i e hemiparesis on the left and at other times on the right) suggests the diagnosis When this is associated with dimness of vision throughout visual fields dysarthria dysphagia or vertigo diagnosis of intermittent insufficiency of the basilar arterial system is probably correct Symptoms are sharply episodic Relief following anticoagulant medication may offer a clue to pathogenesis Present evidence indicates that the prognosis is relatively serious

Cerebral Vascular Disorders Russell Brain[7] (London) analyzed 200 cases of cerebral vascular disease with special reference to age distribution nature of the lesion and correlation between the two About half the patients were over 60 and a fourth under 50

Intracranial aneurysm or an intracranial angioma was found in 16% of the patients Many of them were hospitalized because of subarachnoid hemorrhage Some with an angioma were admitted for investigation of epilepsy and some with an aneurysm because of symptoms of focal pressure Most of these lesions could not have been diagnosed during life without angiography Cerebral embolism was due to rheumatic heart disease in three cases It was also encountered as a complication of operation on the heart

Five patients had permanent hemianopsia due to migraine An aneurysm of the posterior cerebral artery can be excluded as the cause by angiography When the posterior cerebral artery on one side fails to fill on angiography the most likely explanation seems to be that a spasm of this artery has been followed by thrombosis

Hypertension was present in about 50% of patients Subarachnoid hemorrhage occurred in 15% Hemiplegia or monoplegia was slightly less frequent Epilepsy of late onset was due either to cerebral arteriosclerosis or to cerebral angioma Dementia appeared rarely as the presenting symptom Parkinsonism was found in 4% of cases Minor and often transitory cerebral episodes occurred in 87

Prodromal symptoms of atheroma or thrombosis of the

(7) An I t M d 41 675 681 O t be 1954

internal carotid artery consist of transient attacks of amblyopia in the eye on the affected side sudden and brief loss of consciousness periods of mental confusion and transient attacks of speech disturbance weakness of one limb or the opposite half of the body paresthesias or sensory loss or of focal or even generalized epilepsy

The effects of complete and permanent occlusion are extremely variable There may be no symptoms if a good collateral circulation develops On the other hand massive infarction of the whole area of the hemisphere normally supplied by the vessel may ensue leading to hemiplegia hemianesthesia hemianopsia and when the left hemisphere is affected also aphasia Between these two extremes are patients left with some persistent disability which seems more often to be motor than sensory

One should not hesitate to use angiography if an angioma or aneurysm is suspected or even in the presence of cerebral vascular disease if it is necessary to exclude an intracranial tumor

Anticoagulants are rarely used in cerebral vascular disorders in England The reasons no doubt are the danger that a suspected thrombosis may actually be a hemorrhage and the possibility that hemorrhage may occur from the area of infarction produced by a thrombosis if blood coagulability is lowered

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PERIPHERAL VASCULAR DISEASE

Pulseless Disease Outside of Japan This cryptogenic and uncommon disease a chronic progressive obliterative brachiocephalic arteritis has been observed a number of times outside of Japan despite reports to the contrary according to Erik Ask Upmark[8] (Royal Univ of Uppsala) The great majority of patients are young women The obliterating arteritis involves chiefly the brachiocephalic arteries and the resultant ischemia of the upper part of the body is partially compensated for by development of superficial palpable collateral channels which produce demonstrable rib erosion Extension of the pathologic process beyond

(8) Acta med. s and nav 149 161 178 1954

the proximal aorta occurs and has been demonstrated in visceral arteries and in the lower extremities The carotid sinus is involved with production of the carotid sinus syncope syndrome Easy muscle fatigue and actual intermittent claudication of masticatory muscles are common Neurologic symptoms caused by the ischemia are also common The eye appears to be particularly susceptible and various combinations of retinal changes iris atrophy cataract and corneal opacities are to be found Hypertension is common Enlargement of the heart has been reported in the absence of hypertension however Tachycardia is common

Treatment is unsatisfactory Vasodilators have been used Apparently corticotropin has not been evaluated Supportive care with good general hygiene appears to prolong life

Chronic Subclavian Carotid Obstruction Syndrome (Pulseless Disease) Rodrigo A Bustamante Bernardo Milanes Ramon Casas and Angel De La Torre[9] (Havana) describe four cases of occlusion of the great supra aortic vessels and from their data and a review of the literature summarize the symptoms of this disease

Anatomically the syndrome consists of obliteration of the great arterial trunks originating from the aortic arch—the innominate artery left primary carotid and left subclavian The slow obliteration of these trunks causes chronic ischemia of the head and upper limbs evidenced by atrophy of facial muscles orthostatic syncope general or localized epileptiform crises intermittent claudication of the masticator muscles visual disorders transitory amaurosis cataracts optical atrophy atrophy of the iris weakness and numbness of the upper limbs disappearance of the carotid subclavian temporal humeral radial and cubital pulses on both sides disappearance or marked diminution of oscillometric pulses in both upper limbs absence of trophic disorders of the hands possible arterial hypertension in the lower limbs and perforation of the nasal septum This is the clinical picture characterizing the final stages of this syndrome however incomplete or partial forms usually lacking in symptoms can be diagnosed and their evolution followed

In one case the authors found punctiform aneurysms in terminal arterioles in the ocular fundus in addition to the aforementioned symptoms suggesting that this syndrome

ogy 5 479 485 Dec mb 1954

and Takayasu disease are the same condition In two cases there was accompanying aortoiliac obstruction a fact previously unreported resulting in total absence of peripheral pulses Arteriosclerosis is postulated as the cause of the condition in these cases

This syndrome may have diverse causes, including arteriosclerosis and syphilis Nevertheless, the most common characteristic seems to be arteritis of unknown origin principally affecting the supra aortic trunks and appearing most frequently in young women It is proposed that the term chronic subclavian carotid obstruction be used to designate this syndrome

Early Diagnosis of Phlebothrombosis with Aid of a New Clinical Test is described by Robert I Lowenberg[1] (New Haven Conn) A sphygmomanometer cuff is placed around the calf or thigh and slowly inflated over 10 15 seconds Normally patients do not register discomfort at pressures less than 180 mm Hg In the presence of phlebitis however considerable pain at much lower levels is experienced The cuff is immediately deflated after the test A positive reponse is considered present when there is a clearcut patient pain response between 60 and 150 mm Hg The test can be repeated and discomfort should be registered at a pressure within 10 mm of the previous test result Pain is always in the segment of extremity covered by the pneumatic cuff

The author has diagnosed 169 cases of vascular disease with the use of this test Its simplicity makes it particularly valuable for screening patients or for daily observation of postoperative recuperation

Treatment of Chronic Leg Ulcers with Absorbable Gelatin Sponge (Gelfoam) Powder Report of 106 Cases is presented by Irving L Milberg and Jesse A Tolmach[2] (New York Univ) All patients were ambulatory and had received unsuccessful local treatment previously The ulcers were packed with sterile Gelfoam and covered with dry gauze then an elastoplast dressing was applied In 86 patients the ulcers healed completely and in an additional 11 they were improved Other patients with multiple or large ulcers were treated with Gelfoam on some lesions or on half of a large ulceration and various medications on the

(1) J A M A 155 1566 1570 Aug 28 1954
(2) Ibid pp 1219 1221 July 31 1954

other lesions or other half of a single lesion The gelatin sponge powder was the more effective causing earlier formation of granulation tissue and more rapid healing Curetting the margins of the ulcer hastened healing in these instances the hemostatic properties of the Gelfoam materially contributed to improvement of the lesions

Prolonged Anticoagulant Therapy with Subcutaneously Administered Concentrated Aqueous Heparin Hyman Engelberg[3] (Los Angeles) states that heparin is a physiologic substance with a great margin of safety between the therapeutic dose and that producing spontaneous hemorrhage It is effective easily controlled may be used during pregnancy is rapidly neutralized by the infusion of whole blood or by injection of protamine sulfate and has few contraindications

Concentrated aqueous heparin (200 or 100 mg/cc) given subcutaneously to 25 patients uniformly afforded excellent anticoagulation in doses of 125 150 mg every 12 hours In the 200 mg/cc concentration subcutaneous doses of 250 300 mg administered once in 24 hours were usually adequate Aqueous heparin was easy to administer and caused few painful reactions Once an adequate heparin dose has been set with one or two coagulation time determinations further determinations are not required

Apart from its efficacy and safety as an anticoagulant the other known actions of heparin contribute to making it the drug of choice in prevention and treatment of thromboembolic disease It has been shown that heparin lowers blood viscosity that this occurs within a few seconds if it is given intravenously and that the alteration in viscosity persists longer than the decrease in coagulation time Heparin 100 mg intravenously or subcutaneously was also found to lower platelet adhesiveness promptly whereas dicumarol® was ineffective despite good hypoprothrombinemia Increased platelet adhesiveness occurs following parturition surgery trauma arterial occlusion cancer and myocardial or pulmonary infarction

Treatment of Superficial Thrombophlebitis with Phenylbutazone (Butazolidin)® Irwin D Stein (Columbia Univ) and O Alan Rose[4] (New York Univ) treated 33 patients

(3) S g y 36 762 770 O t be 1954
(4) A M A A h I t Med 93 899 905 J 1954

all but 2 of whom had been on bed rest for two to six weeks Dosage was 200 mg three times daily for three days then 200 mg twice a day The drug was discontinued if there was no definite improvement within 48 hours Conditions treated included inflamed varicosities (22), superficial phlebitis without varicosities (3) migratory thrombophlebitis (1) thromboangiitis obliterans (3) and superficial phlebitis associated with malignant disease (4)

Improvement in all patients was uniform and striking No previous method in the authors experience produced as rapid or satisfactory an effect The effect was particularly impressive in that improvement followed unsatisfactory response to other types of treatment In nonhospitalized patients all previous therapy was abandoned and the drug was given with the patient ambulant and without special instructions other than to report immediately any untoward manifestations denoting drug sensitivity Blood cell counts were made only for patients who took the drug longer than one week No allergic reactions were observed but one attack of renal colic was possibly attributable to the drug In three cases although remission was prompt and complete there was a tendency to recurrence and large doses (totals of 7 7 and 15 Gm) were used as suppressive treatment

Because of possible toxic effects phenylbutazone should be used with caution but under competent and constant supervision particularly with short and limited treatment periods it can be used with relative safety Because of its analgesic and anti inflammatory action it may have an important place in treatment of thrombophlebitis

Use of Dibenzyline® as a Vasodilator in Patients with Severe Digital Ischemia has proved to be of value in the experience of Dale G Friend and Edward A Edwards[5] (Boston) This adrenergic blocking agent is related to dibenamine® and is effective both intravenously and orally The drug was given orally in daily doses of 5 80 mg to 23 patients with digital ischemia Fourteen had Raynaud's disease 1 had a minor causalgia and 8 had organic rather than spastic vascular disease including remittent necrotizing acrocyanosis early sclerodermа po tembolic ischemia major artery obstruction and arteriosclerosis

The patient with vasospasm had pronounced benefit all

(5) A M A Arch I t. M d 93 9 8 937 J n 1954

those with Raynaud s disease experienced warmth of the hands and feet abolition of paroxysms of vasospasm and relief from the pain due to ulcerations of the finger tips with healing of the ischemic lesions Similar relief was obtained in some patients with organic arterial disease Three patients—one with causalgia one with acrocyanosis and one with diabetes and arteriosclerosis who had residual sympathetic activity after bilateral lumbar sympathectomy—were not benefited

Nasal stuffiness was a constant side effect but was fairly well relieved by decongestant medications Dizziness weakness nausea and postural hypotension were occasionally observed Drowsiness was frequently present but was overcome with dextroamphetamine Blurred vision occurred in one patient and others had tachycardia

The authors consider dibenzyline® an effective medication as demonstrated in this rather rigorous test It may be useful in the management of patients with arterial insufficiency in the upper extremities where surgical sympathectomy is technically difficult

Effects of Adrenergic Blocking Agent (Dibenzyline®) on Clinical Manifestations of Arterial Insufficiency in the Extremities are discussed by Lothar Wertheimer Walter Redisch and J Murray Steele[6] (New York) with particular reference to healing of ischemic ulcers and relief from intermittent claudication Dibenzyline® was given orally to 28 patients in dosages of 20-480 mg daily Thirteen had ulcers caused by Raynaud s disease thromboangiitis obliterans or obliterative arteriosclerosis 11 had obliterative arteriosclerosis and intermittent claudication without gangrenous ulcerations and 4 had ulcers attributed to impaired venous circulation Criterion of adrenergic blockade was nonreactivity of the constricted pupil to dark or to 10% neosynephrine® Skin blood flow and muscle blood flow were estimated

Healing of the ischemic ulcers in the 13 patients was greatly enhanced and in 2 both of whom had gangrene of the toes necrobiosis was arrested and the gangrene kept dry and mummified Objective improvement (increase in exercise tolerance) was found in four patients with claudication three had subjective improvement (exercise tests not

(6) C cul t on 10 366-373 Sept mbe 1954

being performed), and four had neither subjective nor objective improvement All patients with nonischemic ulcers failed to benefit

After four weeks of adrenergic blocking, average skin temperature of the toes had risen significantly but returned almost to basic values after three to five months of continued treatment blood flow through the skin showed a similar response pattern In contrast, blood flow through muscle showed no significant change after four weeks (except for slightly decreased reflex response to warming) but there was a measurable increase in muscle flow after three to five months This paralleled the more dramatic and rapid relief from ulceration as compared with intermittent claudication

Side effects sufficient to preclude treatment occur in about 1 in 15 patients In this study they consisted of tachycardia occasional auricular fibrillation and in two patients dizziness and confusion

Clinical Trial of Ilidar® a New Dibenzazepine Adrenergic Blocking Drug in Treatment of Peripheral Vascular Diseases and Miscellaneous Complaints in 86 patients is reported by Harold D Green and Hugh H DuBose[7] (Bowman Gray School of Medicine) The drug was given orally in doses ranging from 25 mg three times daily to 150 mg six times a day and the patients were studied for tolerance side effects and toxicity Since other preparations and procedures were used concurrently objective evaluation of the effect of the new preparation on the vascular disease is not possible One patient reported worsening of symptoms with use of the drug The drug appeared generally beneficial however and the vasospastic disorders seemed particularly improved

The drug was well tolerated in therapeutically effective oral doses by 74 patients One could not tolerate it in any amount and reacted consistently with nausea vomiting and drug fever In 35 patients the dose was increased until side effects were noted These commonly consisted of dizziness nausea weakness syncope and drowsiness There were no apparent long term cumulative effects and bone marrow depression did not occur The dosage recommended by

(7) Circulation 10 374 383 September 1954

the authors for most patients is 50 75 mg three or four times daily

Thromboembolic Disease Complicating Pregnancy and Puerperium John C Ullery[8] (Pennsylvania Hosp) analyzed 9 cases of antepartum venous thrombosis occurring in 50 332 pregnancies an incidence of 0 018% and reviewed 126 cases from the literature with results of therapy Owing to the rarity of the condition it is difficult to be dogmatic as to treatment None of 38 patients treated with anticoagulants died but mortality was 15% among those not so treated Anticoagulant therapy is believed safe provided meticulous control of prothrombin time is maintained

Obstructing thrombophlebitis and nonobstructing venous thrombosis are more common after delivery They may be precipitated (1) spontaneously with no known cause (2) following febrile disease or infections (3) following operative obstetric procedures and (4) after trauma

During the puerperium venous thrombosis developed in 172 of the Pennsylvania Hospital patients (0 34%) 7 of whom died There were 51 patients (30%) who were delivered by cesarean section indicating an increased hazard of venous *thrombosis following abdominal delivery* The relative incidence of venous thrombosis was lower in patients who had regional anesthesia during delivery than in those who had general anesthesia

Treatment consists of elevation of the affected extremity and use of heat or elastic bandages in conjunction with anticoagulants or surgery Anticoagulant therapy has largely replaced ligation Therapy is usually started with 50 mg heparin intravenously and 300 mg dicumarol® orally given at the same time the latter being repeated after 24 hours Prothrombin time should be determined daily and be kept close to 20% of normal Rapid subsidence of symptoms and signs has been the rule and patients can be ambulatory in a few days Anticoagulant therapy should be continued until full activity *usually 10 14 days*

Patients with puerperal sepsis or septic abortion with multiple septic emboli are best treated by iliac or vena cava ligation

Prevention of postpartum thromboembolic disease lies in

(8) Am J Obst & Gynec 68 1243 1 60 November 1954

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(7) C c lat on 10 374 383 Sept mbe 1954

generalized lipid disorder with mesenchymal dysplasia and the family history suggest an inborn hereditary defect

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THE KIDNEY

Continuous Therapy of Nephrotic Syndrome in Children with Corticotropin Gel is described by Arthur J Merrill Joseph Wilson and Lloyd F Timberlake[1] (Atlanta Ga) who have used this treatment in 25 patients

PROCEDURE —A daily dose of 1 mg /lb corticotropin is given until albuminuria has been absent for one to two weeks If there is no response after three weeks the dose is increased to 1.2 mg /lb At this time the same dose is given every other day During the subsequent month the amount of each dose is cut about 3% of the original dose during the next month 1 5% of the original dose 0 5% each dose for the next month and finally 1 mg /lb is given twice a week This level is continued for several weeks to allow a period of observation A 200 mg sodium diet is maintained until all signs of Cushing's disease are gone Three to 5 Gm potassium chloride is given during the same period Prophylactic sulfadiazine 0 5 Gm daily is given until the patient has been well for six months Each attack of coryza or pharyngitis is treated with penicillin and the corticotropin dose is doubled until the infection subsides Ears throat chest and abdomen are checked for infection before each injection If relapse occurs indicated by 2-4+ albuminuria either the dosage or the frequency of administration is doubled at once If albuminuria has not diminished within 48 hours the do e is increased to the initial level

All but two children became free from edema and all but three free from albuminuria One patient has been completely unresponsive Although relapses have occurred the course of 24 patients suggests that all will be well eventually Most patients can resume full activity in two to six weeks when albuminuria has disappeared

This form of therapy appears to be more satisfactory than intermittent courses though there is no evidence that the underlying process is cured or even shortened Progressive renal failure and death have not occurred so far during more than two years of observation

Prolonged Intermittent ACTH and Cortisone Therapy in Nephrotic Syndrome Immunologic Basis and Results Kurt Lange Lawrence Slobody and Ruth Strang[2] (New York

(1) A M.A Arch I t. Med 94 925 930 Decembe 1954
(2) Ped trics 15 156-168 F bru y 1955

better antepartum care mature obstetric judgment at delivery and avoidance of venous stasis Early ambulation and treatment of infections are mandatory

Angiokeratoma Corporis Diffusum a rare skin condition is characterized by widely disseminated pinhead purple spots consisting of dilated capillaries surmounted by hyperkeratotic epidermis In three reported cases there were associated cardiovascular and renal abnormalities pains in the hands and feet leg edema and mild hypertension In one case autopsy showed thickening of the muscular layer of the arterial walls of the kidneys adrenals liver spleen lungs heart and skin with vacuolation of the muscle cell cytopla m in the tunica media Widespread deposition of a lipid related to sphingomyelin has also been demonstrated J H Price[9] (Royal Infirm Manchester) reports a case of angiokeratoma corporis diffusum with some unusual associated growth defects

Man 23 had a nonirritant rash on the buttocks abdomen and scrotum present as long as he could remember He complained mainly of stinging and burning pain in fingers and toes absence of sweating and swelling of ankles and feet particularly in warm weather Rapid changes in environmental temperature and exercise initiated attacks of pain which could be relieved by cooling the fingers and toes and bed rest The patient was the 4th of six brothers all 5 ft 10 in tall whereas he was 5 ft 3 in His mother s brother had had tingling pains in the feet and died of renal disease at age 35

Outstanding features were the skin lesions short thick neck and abnormally thick prominent clavicles high pitched voice light beard and short stature The skin was dry and coarse and the rash consisted of small blue red to purple black elevated papules pin point sized to 5 mm in diameter distributed over the entire body except the hands, feet head and neck Rotation of the shoulders and extension of the elbows and fingers were limited He had bilateral pes planus and the ligamentum nuchae was abnormally thick B ood pressure and heart lungs and abdomen were normal There was persistent ankle edema and the feet were constantly dry even in a hot environment Urine examinations revealed epithelial cells red blood cells granular casts and reduced gonadotrophins Roentgenograms showed unusually thick clavicles abnormal cervical vertebrae and incomplete fusion of radial and ischial epiphyses Skin biopsy showed slight hyperkeratosis more marked over dilated capillaries in the papillary layer In one muscle artery from the pectoralis major there was marked vacuolation of the cytoplasm of the cells of the media

The vacuolation of the arterial muscle possibly part of a

(9) Br t J D rmat 67 105 109 M h 1955

the levels of plasma protein and cholesterol and reduction of proteinuria Cortisone therapy did not produce diuresis in four patients but prevented relapses in a high percentage

The rise in serum complement ensuing diuresis and remissions following therapy with these drugs can be explained by the depressant action of ACTH and cortisone on antibody formation

Therapy of Nephrotic Syndrome Sodium Restriction Dextran and Corticotropin (ACTH) Alone or Combined with Nitrogen Mustard Lawrence Greenman F A Weigand and T S Danowski[3] (Univ of Pittsburgh) report a study on 30 nephrotic children most were under 6 years and two thirds were boys Two were edema free on hospitalization

The patients received a calorically adequate diet providing 2 9 mEq sodium about 150 mEq potassium and 5 Gm/protein/kg body weight each day with supplementary iron and vitamins An antibiotic usually penicillin was given prophylactically Two patients received urea before ACTH 18 were given colloid and 6 12 or 20% dextran or 3 5% polyvinylpyrrolidone (PVP) with or without sodium Usually 500 ml was infused each day for four to six hours for a total volume to 7 200 ml ACTH was given intramuscularly 25 mg every six hours for 28 days The last five patients received ACTH alone 25 also had 0 3 mg nitrogen mustard per kg usually on the third day of ACTH therapy All patients were kept at bed rest

Dextran PVP or other methods were used in all but 2 but 14 still had edema when ACTH was started Diuresis occurred in 11 of these after one or two weeks another lost excess fluid gradually over four weeks two had diuresis after ACTH was discontinued Three required paracentesis during treatment At completion of the initial course 12 patients had normal results on urinalysis in 11 only trace or 1+ albuminuria was present with granular casts and microscopic hematuria in 1 7 still had 2-4+ albumin of whom 2 continued to have granular casts 1 with hematuria When ACTH was discontinued nonprotein nitrogen was under 38 mg /100 cc in all but three children

Despite rigid sodium restriction only three patients had sodium concentrations below 132 mEq /L two of these

(3) A M A Am J D Ch ld. 89 169 181 F bru ry 1955

Med College) believing that in glomerulonephritis and the nephrotic syndrome there are complement binding antigen antibody reactions with the kidney as a vast antigenic surface investigated the serum complement levels of patients with these conditions and of controls Results of therapy with ACTH and cortisone were also studied

In 166 controls (100 adults and 66 children) average level of serum complement was 1 78 units with a range of 1 1 3 units and with only 5% of the readings below 1 2 units One complement unit is equivalent to that dilution of 0 1 ml of freshly prepared lyophilized complement which produces 50% hemolysis In 40 cases of acute and subacute glomerulonephritis (21 children 19 adults) average complement level was 0 32 units with a range between 0 and 1 In 29 cases (20 children) of the nephrotic syndrome with or without underlying glomerulonephritis values ranged between 0 2 and 1 4 units These low complement levels were not due to loss of complement into the urine lack of formation or anticomplementary factors

Spontaneous remissions of the nephrotic syndrome were preceded in 11 of 13 instances by high fe er Depression of the eosinophil count (4 patients) and a rise in urinary 17 ketosteroids (1 patient) were also observed In these remissions complement rose before diuresis and fell before relapses further supporting the idea that in these diseases one is dealing with an extensive antigen antibody reaction with immunologic and corresponding clinical variation Furthermore rise in serum complement and diuresis occurred independent of changes in plasma protein levels and plasma oncotic pressure

ACTH 100 mg /day given for 3 8 weeks on 3 successive days of each week after an initial 7 10 day course of ACTH (children 100 mg /day adults 160 mg) was accompanied by long lasting remissions in three of six patients with nephrotic syndrome A rise in complement levels followed by diuresis preceded remissions while the relapses were preceded by a fall in complement

Cortisone orally in doses of 400 mg /day on a similar schedule after an initial 7 10 day course of ACTH was also accompanied by a rise in complement and long remissions in 16 of 18 patients when given for 6 30 courses Cortisone maintenance therapy also led to rapid return to normal of

nine commonly associated with low urinary sodium and chloride concentration Failure of diuretic response could be predicted by finding total 24 hour urinary sodium or chloride excretion under 12 mEq Potassium diuresis occurred in two patients with significant water diuresis (increments of 1 400 and 1 300 cc) without increased sodium and chloride excretion Water diure is alone occurred in seven Failure of diuretic response in five was associated with earlier loss of edema hepatic disea e hyponatruria and renal disease

In general satisfactory clinical response ultimately followed significant diuretic response Polyuria was characterized by moderate increase in frequency nocturia and passage of a large volume with each micturition With the dosage used no toxic side effects were noted Long term toxicity for large (4 Gm) doses given repetitively remains to be evaluated

Formation of Edema and Effect of Sodium on Colloid Osmotic Pressure By subjecting known physicochemical data to abstract analysis Russell H Kesselman[5] (Woman s Med College of Philadelphia) derived a semiquantitative equation which physiologically is descriptive of the functional relation between sodium ion concentration and colloid osmotic pressure Thi demon trates that when character and quantity of plasma protein and plasma pH are kept constant a fall in plasma sodium concentration produces a rise in plasma colloid osmotic pressure and vice versa With diminution of pla ma sodium there is also a fall in diffusible anions mainly Cl and HCO_3

The demon tration of this functional relation gives valuable insight into one of the mechanisms involved in influencing shifts of fluid between different body fluid compartments Edema formation would be favored by elevation of plasma sodium and edema resorption by a lowered plasma sodium This agrees with clinical observations of the role of increased and decreased sodium intake and output in many edematous states

It might be argued that wide shifts in serum sodium concentration are not ordinarily seen in successful treatment of edema of congestive heart failure with low sodium diets ion exchange resins or mercurial diuretics A reduction in plasma sodium level of 10 mM /L (e g from 145 mM to

(5) Am Heart J 49 517 520 Ap 1, 1955

had convulsions with blood pressures of 130/118 and 180/128 Other complications included mental depression peritonitis minor blood pressure elevations glycosuria and hyperglycemia All developed moon facies protuberant abdomens and cervical fat pads

There were six recurrences in two patients who had remained well three to seven months One was re treated once and the other had six courses with clearing of abnormalities each time for 2 10 months Three children among the original group of eight with least improvement were also re treated

At last examination 22 (73%) of the 30 patients had normal results of urinalysis (4 had traces of albumin) 1 with albumin trace had slightly elevated serum cholesterol concentration Biochemical findings were normal in 21 Four had 1 2+ albumin Four (13%) were definitely abnormal two had hypertension three abnormal urine two low serum protein values three increased cholesterol levels and one elevated nonprotein nitrogen

Diuretic Action of Benemid ® Its Effect on Urinary Excretion of Sodium Chloride Potassium and Water in Edematous Subjects Benemid ® 4 Gm /day produced significant diuresis in 13 subjects with uncomplicated congestive heart failure studied by David Bronsky Alvin Dubin and Daniel S Kushner[4] (Northwestern Univ) Mean increment of water excreted on the day of maximal response was 1 330 cc of sodium 91 mEq and of chloride 76 mEq /24 hr Mean weight loss was 7 lb (range 0 16 lb) at the end of the seven day test period Maximal response occurred on the first day in seven on the second in four In two water diuresis occurred the day after the drug was discontinued In all but two maximal diuresis of water sodium and chloride occurred within the same 24 hour period Serum sodium chloride and potassium levels showed no change Concentration of urinary sodium and chloride significantly increased despite rise in urinary volume in 11 of 13 patients In one with arteriosclerotic heart disease congestive heart failure and chronic gouty arthritis with hyperuricemia serum uric acid level was lowered and urinary urate excretion rose

Twelve failed to respond to benemid® with augmented excretion of sodium and chloride Oliguria was prominent in

(4) Am J Med 18 59 266 F b uary 1955

chromatography sodium retaining material was found in a single fraction E Its active component was shown to be aldosterone in one case and it is probable that the sodium retaining corticoid in the other cases was also aldosterone

Correction of Electrolyte Deficits in Cardiovascular Renal Disease and in particular use of hypotonic solutions are discussed by F R Schemm and A A Camara[7] (Great Falls Mont) Salt losing nephritis represents the inability of damaged tubules to reabsorb filtered sodium In such cases supplementary sodium is required to maintain balance Potassium loss is significant in cardiac patients and nephritics with previously manageable edema who become refractory to treatment with diuretics and patients with far advanced kidney disease who may become potassium losers spontaneously Patients in the first group may respond again to treatment with potassium salts Potassium chloride may be given intravenously (2 4 Gm /L of 5% glucose) or orally buffered with calcium carbonate or potassium bicarbonate may be used Hypokalemia may characterize end stage kidney disease rather than the hyperkalemia more frequently reported Tubular secretion of potassium may persist particularly if the sodium intake is such that there is an internal stimulus to conserve it a serious potassium deficit may follow

Reabsorption of sodium is controlled by the adrenal cortical hormone and that of water is governed by the antidiuretic hormone of the posterior pituitary the co ordinated activity of these centers produces homeostatic reabsorption The site of the co ordinating mechanism is unknown When this co ordination is not maintained water may be retained excessively In patients who are resistant to mercury diuretics with resulting edema and hyponatremia administration of sodium chloride—concurrent with or followed by a mercurial diuretic—may cause dramatic fluid loss

In desperate cases patients have been given corticotropin and the authors have found that despite its accepted effect on electrolytes it appears to cause a spontaneous profuse diuresis of sodium or water on the third to sixth day after administration (15 25 units every 6 hours for 10 12 days) or in some way alters the response to mercurial

(7) Circ 1 t on 10 430 441 S pt mbe 1954

135 mM/L) will raise plasma colloid osmotic pressure by 10 mm water an amount which could well result in major shifts of body fluid Another perhaps more important reason why wider shifts in serum sodium concentration are not observed is that body fluid compartments are close to if not at equilibrium with each other and are in no way closed systems The role of the kidney is particularly important In a situation in which a small amount of sodium might be removed or lost from plasma the concentration of plasma sodium would then be lower and plasma colloid osmotic pressure would be elevated Fluid would shift from the interstitial fluid compartment to the intravascular compartment (plasma) The kidneys might rapidly move additional water from the plasma to elevate the lowered plasma sodium concentration However the precise sequence of events is really not known

Aldosterone in Urine of Normal Man and of Patients with Edema Its Increased Recovery after Hydrolysis with Acid and with Beta Glucuronidase Studies have shown that neutral lipid extracts of acidified urine from patients with the nephrotic syndrome in heart failure and in some other edematous states cause sodium retention and potassium elimination when injected into adrenalectomized rats The amount of this sodium retaining corticoid that can be extracted from urine by chloroform is shown by B J Axelrad J E Cates B B Johnson and J A Luetscher[6] (Stanford Univ) to depend partly on the method of hydrolysis Of the procedures *studied the greatest yield was obtained from* urine after standing for one day at pH 1 Smaller quantities were obtained after brief exposure to pH 1 or after incubation at 37 C and pH 4 8 Mammalian beta glucuronidase caused further release Insignificant activity was found in extracts from urine at pH 6 5

In health on unrestricted sodium intake the sodium re*taining* activity of urinary extracts is small but still measurable Reduction of dietary sodium to 11 mEq/day for five days was followed by increased sodium retaining activity Patients with congestive heart failure hepatic cirrhosis or the nephrotic *syndrome had a high output of sodium* retaining material when urinary sodium was low

In all cases in which urine extracts were studied by

(6) *B t M J* 1 196-199 *J n* 22 1955

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(7) Circulation 10 430-441 September 1954

diuretics In a few edematous patients it has appeared to correct hyponatremia without supplementary dietary sodium The authors do not present this use of corticotropin to commend it for any except the near hopeless cases and in these it must be given with meticulous observation

The authors warn against preoccupation with electrolyte concentration at the risk of overlooking deficit in total body water which may be of more significance In certain patients hypotonic saline solutions have produced remarkable responses in fluid and electrolyte imbalances after such events as prolonged gastric suction Hyponatremia does not always indicate dilution of extracellular fluid It may coexist with a high plasma specific gravity and may be corrected by solutions hypotonic with regard to sodium

Medical Management of Advanced Renal Insufficiency is discussed by Arnold S Relman[8] (Massachusetts Mem l Hosp Boston) Because there is some evidence that the course of chronic glomerulonephritis is punctuated by recurrent respiratory infections with beta hemolytic streptococcus it may be wise to give penicillin to all patients with this disease Relman s current practice is to give 100 000 units orally twice daily throughout the year

Urinary infections should be recognized and treated Since in practically all patients with indwelling catheters and gravity drainage urinary infections develop regardless of antibiotic prophylaxis these procedures should be restricted to the minimum

In uremia the dosage of sulfonamides and streptomycin should be reduced but most other antibiotics can be given in full amounts Bacitracin and neomycin are contraindicated Therapy should be selected with regard to the specific sensitivities of the organisms involved and should be continued until the urine has become sterilized or the pathogenic bacteria have become resistant

Sodium restriction is of dubious value in nonedematous patients Severe dehydration with hyponatremia calls for isotonic sodium solutions severe hyponatremia with little or no dehydration requires hypertonic (2 5%) sodium solutions When dehydration is extreme and sodium concentration normal hypotonic sodium solutions (made isotonic with glucose) are needed

(8) M Clin North Amer 33 1447 1460 Sept mbe

Severely azotemic patients usually do not have nephrotic but cardiac edema In adults with coexisting nephrotic syndrome and chronic uremia the prognosis is generally poor because these conditions are usually seen only in rapidly progressing glomerulonephritis or in intercapillary glomerulosclerosis Marked azotemia almost always prevents effective use of diuretics Cortisone and ACTH are ineffective and may be hazardous in patients with advanced renal failure and edema The physician can only restrict dietary sodium as rigidly as possible

It is a fairly safe generalization that when the CO_2 concentration is below 15 mEq/L most patients will benefit from treatment of acidosis Relman gives 100-150 mEq sodium bicarbonate or lactate on the first day of treatment depending on the severity of acidosis and then uses the observed rise in plasma CO_2 as a guide to further therapy

In hyperpotassemia excess potassium may be removed from the gastrointestinal tract by exchange resins

Anemia is almost invariably present in chronic uremia The only effective way to increase the hemoglobin concentration is to give slowly 200 300 cc of packed fresh red cells at a time

Reduction in protein catabolism helps prevent many of the electrolyte disturbances of uremia as well as the rise in blood nitrogen level A diet containing 30-40 Gm protein daily will usually keep an adult in nitrogen balance if the total caloric intake is adequate

In congestive heart failure digitalis should be given in doses similar to those used in patients without uremia Ammonium chloride should not be used because of the danger of severe acidosis Fluid should be restricted only in patients with massive edema and hyponatremia

Convulsion usually can be controlled by short acting barbiturates (sodium amytal®) parenterally

Successful Use of Simplified Method of Intermittent Peritoneal Dialysis William H Waugh[9] (State Univ of New York Brooklyn) presents the thesis that intermittent peritoneal lavage can be used in human beings for extended periods without development of peritonitis or other serious complications

(9) J U 72 1095 1103 December 1954

diuretics In a few edematous patients it has appeared to correct hyponatremia without supplementary dietary sodium The authors do not present this use of corticotropin to commend it for any except the near hopeless cases and in these it must be given with meticulous observation

The authors warn against preoccupation with electrolyte concentration at the risk of overlooking deficit in total body water which may be of more significance In certain patients hypotonic saline solutions have produced remarkable responses in fluid and electrolyte imbalances after such events as prolonged gastric suction Hyponatremia does not always indicate dilution of extracellular fluid It may coexist with a high plasma specific gravity and may be corrected by solutions hypotonic with regard to sodium

Medical Management of Advanced Renal Insufficiency is discussed by Arnold S Relman[3] (Massachusetts Mem l Hosp Boston) Because there is some evidence that the course of chronic glomerulonephritis is punctuated by recurrent respiratory infections with beta hemolytic streptococcus it may be wise to give penicillin to all patients with this disease Relman s current practice is to give 100 000 units orally twice daily throughout the year

Urinary infections should be recognized and treated Since in practically all patients with indwelling catheters and gravity drainage urinary infections develop regardless of antibiotic prophylaxis these procedures should be restricted to the minimum

In uremia the dosage of sulfonamides and streptomycin should be reduced but most other antibiotics can be given in full amounts Bacitracin and neomycin are contraindicated Therapy should be selected with regard to the specific sensitivities of the organisms involved and should be continued until the urine has become sterilized or the pathogenic bacteria have become resistant

Sodium restriction is of dubious value in nonedematous patients Severe dehydration with hyponatremia calls for isotonic sodium solutions severe hyponatremia with little or no dehydration requires hypertonic (2 5%) sodium solutions When dehydration is extreme and sodium concentration normal hypotonic sodium solutions (made isotonic with glucose) are needed

(8) M Cl n N rth Am i a 33 1447 1460 S ptember

fluid and nutrition via this route with no technical difficulties She recovered fully

For infusion into the inferior vena cava a 2 in incision is made over the upper end of the saphenous vein the vein is exposed and its tributaries are ligated The vein is opened and a polyethylene catheter 4 mm in diameter is introduced for 8 10 in and secured with a double ligature of fine catgut At the time of insertion in the present case a heavy Nylon suture was passed through the skin under the saphenous vein ½ in proximal to the point of entry of the catheter over the vein and then again under it and thence out through the skin of the opposite side The suture was tied over a piece of gauze with the ends left long When the catheter was removed the Nylon suture was tightened thus kinking the vein and preventing bleeding It was removed by traction 72 hours later

Inferior vena cava infusion is preferred to superior vena cava infusion because the site of entry of the catheter is less likely to be interfered with by movement and the distance traversed in small veins is minimized

Chronic Renal Insufficiency Appraisal of Patient Treatment It is the premise of James Hopper Jr Alfred Bolomey and R Wennesland (Univ of California) that given sufficient time the lesions of chronic kidney disease may heal in a manner comparable with the healing of acute renal changes Appraisal of the patient by history and careful physical examination may define the etiologic lesion and will often influence therapy Urinalysis of a freshly voided acid urine is comparable with a biopsy

The main principle in treatment of chronic renal insufficiency consists of maintenance or restoration of normality of volume and concentration of body fluids This is comparable with digitalis administration to the failing heart the anatomic defect is unaltered but efficiency is enhanced Edema is uncommon in uncomplicated chronic renal insufficiency When it exists usually in conjunction with other disease correction may be difficult Mercurial diuretics and concentrated human albumin may be used judiciously Cortisone and ACTH have not been shown to produce diuresis or improve renal function in these patients Nitrogen mustard is too toxic for general use and other diuretics are apt to produce toxic effects The dispute between advo

(2) A I t. M d 41 18 35 J ly 1954

Technic—The lavage fluid consists of lactated Ringer's solution USP with glucose added to a final concentration of 2-6 Gm/100 ml. Penicillin (50 000 units) and streptomycin (0 5 Gm) are added to each liter of fluid

Paracentesis is performed in the midline below the umbilicus of the supine patient The stilet is removed and tubing from an intravenous infusion set attached to the proximal end of the trocar The lavage fluid preferably at body temperature is instilled during a brief period to a total volume of 3-3 5 L The trocar is withdrawn a plug inserted into the superficial part of the paracentetic opening and a sterile pressure dressing applied.

Within two to four hours dressing and the plug are removed with the patient sitting The trocar is then reinserted at the same site without anesthesia and paracentetic drainage is accomplished by gravity The site is redressed The procedure is repeated as necessary even two to three times daily

This method was used in a boy 14 with acute glomerulonephritis and uremia Over 29 days he had 45 intermittent peritoneal dialyses with good results He died of myocardial infarction and heart failure There was no peritonitis

Intermittent peritoneal dialysis using a lactated sodium chloride solution is advocated for alleviation of potassium intoxication if it is severe despite conservative therapy Sufficient glucose should be added to make the lavage solution somewhat hypertonic to the patient's plasma Besides removing sizable amounts of potassium this dialyzing fluid may also lessen the toxicity of hyperkalemia due to its excess amount of sodium ion

Prolonged Anuria Successful Management by Continuous Infusion into Inferior Vena Cava is described by C Scott Russell C J Dewhurst and J C Brace[1] The method is neither formidable nor dangerous

Woman 31 had had a septic abortion followed by anuria and oliguria for about three weeks Intractable vomiting made gastric feeding unsatisfactory and to achieve adequate caloric intake without fluid overload it was decided to infuse 40% glucose solution into one of the large veins thereby minimizing the danger of thrombosis which would follow use of a small caliber vein A cardiac catheter was introduced into the superior vena cava and hypertonic glucose administered providing 1 600 calories or more daily with a fluid intake of 1 L to offset insensible water loss Phlebitis assumed to be infectious occurred in the basilic vein after four days and the catheter was withdrawn Infusion into the inferior vena cava was then tried A polyethylene catheter was introduced through the right saphenous vein for 8 in and for 17 days the patient received

(1) Lancet 1 90 905 May 1 1954

D daily the chloride bicarbonate and phosphate levels slowly returned to normal and urinary ammonia and amino acid concentration decreased Urinary sugar excretion de creased and a positive phosphorus and calcium balance also followed administration of the vitamin despite increased *renal clearance of calcium Fecal calcium decreased more* than the urinary calcium increased renal clearance of phos phorus declined Clinically the leg pains attributed to osteo malacia were relieved and the patients were again able to walk comfortably

A prolonged follow up will be necessary before adequate evaluation is given The long term effects of hypercalciuria will be particularly observed

There is histochemical evidence of impaired phosphatase activity in the renal tubules of patients with Fanconi s syn drome Water soluble vitamin D has been shown to increase activity of alkaline phosphatase obtained from bone kid ney or gastrointestinal tract These and other observations prompted the authors to estimate the metabolic response to high doses of this vitamin

Potassium Losing Nephritis Presenting as Case of Period ic Paralysis B M Evans and M D Milne[4] (Postgrad Med School London) report a case of chronic pyelonephri tis with severe urinary potassium loss

Woman 41 since 1944 had had attacks of paralysis of the legs and arms lasting 2 20 days and recurring about every 3 months She felt reasonably well between attacks She had had three epi sodes of dysuria and frequency of micturition associated with py rexia in 1945-47 On hospitalization she was unable to move her legs and tendon reflexes were absent Though the arms were ex tremely weak she could move them Sensation was intact Blood pressure was 180/110 and the heart was slightly enlarged Intra venous pyelography showed only a defective concentration of the contrast medium An ECG was typical of hypokalemia The urine showed constant albuminuria and occasional erythrocytes and pus cells Specific gravity was fixed at 1 011 Culture was sterile The glomerular filtration rate was probably about 50% of normal Blood urea was 27-42 mg./100 ml serum albumin 2 9 Gm /100 ml globu lin 4 8 Gm /100 ml and potassium 1 4 mEq /L

Familial periodic paralysis was excluded by the family history and the constant abnormal urinary loss of potassium and Cushing's syndrome was excluded on clinical grounds

A standard diet containing 85 mEq potassium and 140 mEq sodium daily was given together with potassium chloride orally three times a day first 5 Gm later 2 Gm with 1 Gm potassium

(4) B M J 2 1067 1071 Nov 6 1954

cates of low protein and moderate protein diets remains unsettled The University of California Hospital usually supplies a moderate protein intake Replacement of electrolytes should be done as quantitatively as possible The hyperphosphatemia often found in these patients tends to produce hypocalcemia This derangement may often be avoided or corrected by appropriate administration of extra base to spare calcium excretion, use of a low phosphorus diet (0 5 Gm /day or less) and of nonabsorbable aluminum gels to hinder phosphate absorption in the gut and administration of calcium salts The anemia of chronic renal insufficiency is often difficult to treat Small transfusions are beneficial Cobaltous chloride 90-200 mg /day may be of some benefit For peptic ulcer associated with renal insufficiency the authors favor the use of nonabsorbable alkalis, such as aluminum hydroxide gel or aluminum carbonate The judicious use of some of the newer antihypertensive agents such as hexamethonium and 1 hydrazinophthalazine appears to produce favorable results in some cases In encephalopathic crises intravenous use of hexamethonium 1 hydrazinophthalazine and veratrum appears particularly effective Sedatives are often necessary but those excreted by the kidney should be used with caution In most cases of chronic renal insufficiency life can be prolonged and normalcy at least partly restored

Observations on Metabolic Effects of Vitamin D in Fanconi s Syndrome are reported by Robert M Salassa Marschelle H Power John A Ulrich and Alvin B Hayles[3] Sodium bicarbonate ammonium chloride and vitamin D were given successively to two children aged 16 and 11 The syndrome characterized by high renal clearances of phosphate and glucose hypophosphatemia aminoaciduria hyperchloremia and acido is high urinary ammonia and increased titrable acidity with normal serum calcium and blood urea concentrations is considered a congenital metabolic defect generally unresponsive to treatment Therapeutic trials of sodium bicarbonate tended to correct the low plasma bicarbonate and high plasma chloride levels with a decrease in urinary ammonia and acidity However hypophosphatemia and aminoaciduria were unaltered Ammonium chloride administration was ineffective With 400 000 units of vitamin

(3) Proc Staff Meet M y C n 29 214 2 4 Apr 21 1

intakes according to blood analyses Complete recovery of renal function may occur in days or months

Treatment during acute shock is aimed at restoration of blood volume and general and renal circulation before renal ischemia has lasted long enough to produce tubular *damage Blood that has been lost should be replaced* When desiccation is the cause of shock saline infusions are indicated Overadministration of fluids can cause immediate death from embarrassment of cardiac action or pulmonary edema

During the oliguric period the aim is to keep the patient alive long enough for the kidneys to recover function Water is given only to balance the loss by skin lungs and the small volume of urine As soon as food is tolerated a fat carbohydrate electrolyte free diet is given to minimize tissue catabolism and resultant release of nitrogen products potassium sulfate and phosphate in the blood Hyperpotassemia may be counteracted by insulin and glucose and by oral administration of ion exchange resin in the sodium phase

The close observation required during the oliguric period should be continued during the diuretic phase until the kidneys can maintain normal body hydration and normal urea and electrolyte plasma concentrations in the face of ordinary variations of water and food intake

In acute and chronic stages of glomerular nephritis the glomeruli as well as the tubules are involved Retention of nitrogenous products is related to glomerular damage but water and electrolyte disturbances are largely attributable to the tubules and probably cause the syndrome of uremia

Congenital Hereditary Hematuria a rare but established disease is reported in eight members of four unrelated families by Gertrud C Reyersbach and Allan M Butler[6] (Harvard Med School) The syndrome consists of hematuria cylindruria and albuminuria in this series and in some previous reports it was also accompanied by nerve deafness Congenital eye defects may be present The genetic aspects are incompletely appraised generally it appears to be a dominant trait transmitted (not always) by females and

(6) N w E gl d J M d 251 377 380 S pt 25 1954

citrate She was discharged in a state of moderate hypokalemia Muscle strength was much improved She has remained fairly well during four months of outpatient observation On maintenance dose of potassium chloride and citrate only short periods of muscle weakness or hypokalemia occurred and were helped by increasing the dosage

This case is probably one of the most severe example of potassium loss from pyelonephritis The original total deficit of potassium was likely about 1 500 mEq which is just over 40% of the patient s expected total body content of potassium Balance data show that most of the intracellular potassium deficit had been replaced by a large increase of intracellular sodium About 70% potassium was replaced by sodium

Renal Tubular Failure of Shock and Nephritis is discussed by Donald D Van Slyke[5] (Brookhaven Nat l Lab) Renal tubular failure occurs in many clinical conditions which have in common one factor a decrease (lasting usually for several hours) in volume of circulating blood usually to such an extent that signs of shock develop The cause may be hemorrhage trauma burns the desiccation of vomiting dysentery or diabetic coma or cardiac failure Organic renal damage is evidenced by failure of renal function to recover when general circulation is restored Functional and histologic evidences both indicate that the organic damage is tubular The functional effect may vary from moderate decrease in urea clearance to anuria ending in uremia

In animal experiments progressive hemorrhage was found to lead to vascular constriction in the kidneys This caused first an increase in the filtered fraction probably due to efferent constriction Eventually ischemia injured the tubular cells and caused the tubular failure that follows severe and prolonged shock

Shock causing renal damage is followed by a period of anuria or oliguria the small volume of dilute urine excreted for a number of days tends to approach plasma ultrafiltrate in electrolyte and urea concentrations Plasma urea and potassium concentrations increase Later if diuresis occurs there may be indiscriminate output of plasma electrolytes and water and it becomes necessary to regulate

(5) An I t. M d 41 09 738 O tob 1954

interval the abdominal aorta was exposed and ligated on each side of the origin of the renal arteries and 500 ml normal saline was perfused through the abdominal aorta At the end of the perfusion the return in the inferior vena cava was colorless The kidneys were removed and homogenized in a mortar with 5 Gm sea sand and 6 ml distilled water 25 ml of 1% aerosol OT was added and the mixture allowed to stand for 30 minutes The dye was eluted from the kidneys by this procedure and then precipitated in the eluate by the addition of 50 ml acetone The precipitate was extracted again in a similar manner

In other animals to determine the dye protein serum ratio concentrations of dye and protein were determined at desired times following severing of the aorta

Calculations showed that protein is reabsorbed at the rate of 4 6 mg /hour for the first four hours (mean rate 5 mg /hour) following this the reabsorption rate levels off at approximately 2 mg /hour The glomerular filtration rate of 200 Gm rats is 72 ml /hour and protein is excreted at a rate of about 0 5 mg /hour Hence if protein is being reabsorbed at a rate of 5 mg / hour then 72 ml glomerular filtrate would contain 5 5 mg protein or 7 6 mg /100 ml The circulating blood volume of a 200 Gm rat is about 15 ml and the hematocrit value about 60% If the plasma protein concentration is 6 Gm /100 ml there is a total of 360 mg circulating plasma protein The rat filters reabsorbs and presumably metabolizes about 120 mg protein daily or a third of its circulating protein

Recurring Renal Disease Caused by Endogenous Ovarian Hormone Ralph Reader and L C Watson[8] (Univ of Sydney) present a case of renal disease apparently caused by hormonal allergy

Girl at age 18 had the first of a series of attacks which began with an erythematous rash generally located over the trunk and upper thighs and progressively became annular or serpiginous Individual lesions had a slightly raised edge and occasionally a pale center The rash was never weeping or pruritic Within a few hours of onset fever headache malaise anorexia hypertension proteinuria and hematuria developed The blood urea nitrogen became elevated during the attacks but usually returned to normal after they ceased Occasionally palpitation limb or joint pains arthritis iritis and episcleritis were present The attacks spontaneously subsided in 8 10 days without treatment The renal disease was progressive and after several months of recurring attacks proteinuria isosthenuria hypertension and uremia became constant The occurrence of the attacks at the midmenstrual period suggested a relation to ovulation or estrogen and intradermal injections of

(8) A tral A Med 3 116-1 M y 1954

affecting both sexes although clinically it may be worse in males The abnormal urinary constituents are present in infancy with intermittent exacerbations often occasioned by infectious diseases There may be abdominal pain and vomiting Renal biopsy on a 2 year old patient disclosed no abnormality other than blood in the tubules Glomerular disease did not seem to be present although it could not be excluded The disease is relatively benign although progressive kidney impairment may occur A tendency to hypertension toxemia and edema during pregnancy has been reported

The disease is of importance both as a cause of occasional chronic kidney disease and for differential diagnosis of other renal disorders The pathologic physiology has been insufficiently studied Treatment is ineffective Cortisone 20 mg/day failed to alter the hematuria in one patient but the trial was inconclusive because of small dosage and repeated infections during therapy

Filtration and Reabsorption of Protein by the Kidney was estimated in rats by Alvin J Sellers Neilyn Grigg Jessie Marmorston and Howard C Goodman[7] (Los Angeles) T 1824 being used to tag the plasma protein This dye forms a stable blue complex with plasma proteins preferentially albumin It is assumed, with some corroborative experimental evidence that this dye protein complex behaves in vivo essentially as does the unaltered protein When 25 mg T 1824 is injected intravenously into 200 Gm rats no measurable free dye is found in the blood and when proteinuria is produced all the dye found in the urine is protein bound The authors reason that the dye present in the lumen of the nephron is protein bound and that the complex dye protein is reabsorbed by the cells of the proximal convoluted tubule where it can be seen microscopically in the form of droplets Extraction and measuring of the dye of the tubule cells and determination of the mean ratio of T 1824 to protein per unit time in the plasma give information from which the milligrams of protein reabsorbed by the kidney during any time interval can be calculated

METHOD —All animals received 20 mg T 1824 in 1 ml saline intravenously Bleeding was done under ether anesthesia by severing the abdominal aorta The total T 1824 content of the kidney was determined in the following manner At the end of the desired time

(7) J Exper Med. 100 1 10 July 1954

The Digestive System

FRANZ J INGELFINGER MD

1 2 mg stilbestrol consistently provoked identical attacks ACTH relieved an attack within a few hours Bilateral oophorectomy was performed because of renal deterioration and no attacks have occurred in the nine months since operation

Evidence suggesting that this was an antigen antibody disease is found in the composite clinical picture which contained some of the features of acute nephritis or anaphylactoid purpura erythema marginatum of rheumatic fever and allergic arthritis and iritis The invariable relief following ACTH administration occurred so promptly that it was felt that *an antigen antibody reaction* was suppressed directly Provocation of attacks by synthetic estrogens likewise contributed to the evidence of hormonal allergy The presence of the clinical picture of chronic glomerulonephritis *following the repeated attacks further illustrates* that the acute renal lesion antedating such a clinical syndrome need not be acute glomerulonephritis

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PART V

THE DIGESTIVE SYSTEM

STOMACH AND DUODENUM

Physiology of Gastric Antrum Experimental Studies on Isolated Antrum Pouches in Dogs Edward R Woodward Edward S Lyon John Landor and Lester R Dragstedt[1]

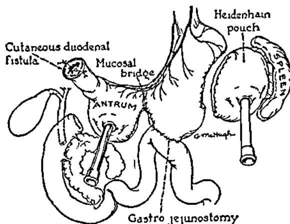


Fig 81 —Isolat f ga t trum w th p rv t on f blood d n rv p ply m l pr p d w th H d h n (d ervated f d) pou h (C rt y f Woodw d E R t l G t t logy 27 766 785 Dec mbe 1954)

(Univ of Chicago) investigated the effect of acid in the antrum on the antral phase of gastric secretion Experiments were performed on four animals using two types of preparations

EXPERIMENT 1 (Fig 81) —In the first animal a Heidenhain pouch was constructed Then the main stomach was separated from the antrum by a membrane of two layers of gastric mucosa Anastomosis

(1) G t oent l gy 27 766-785 December 1954

When the first animal was fed and placed in a Pavlov frame a moderate secretion of highly acid gastric juice was collected from the Heidenhain pouch after about two hours and persisted for six to eight hours Since the Heidenhain pouch had no vagus innervation and the antrum was entirely excluded from the gastrointestinal tract this secretory response presumably represents the intestinal phase

After a constant secretion was obtained from the Heidenhain pouch the isolated antrum was perfused with N/10 HCl No inhibitory effect was noted on seven of eight occasions That the intestinal phase of gastric secretion was not inhibited by the presence of acid in the antrum suggests that (1) hormones mediating the gastric and intestinal phase of gastric secretion are not identical and (2) inhibitory effect of acid applied to the antrum is due to interference with gastrin formation or release and not to formation of an antisecretory substance

In none of the animals did acid in the antrum prevent or alter the secretory response to histamine or inhibit gastric secretion of nervous origin Application of acid to the duodenum in three tests did not inhibit gastric secretion Mechanical distention readily and strongly stimulated the isolated antrum with blood and nerve supply intact to release gastrin It is difficult to understand why acid perfusion of the antrum failed to inhibit this response The local application of cocaine or atropine solutions to the antral mucosa inhibited both spontaneous gastric secretion and the response obtained by instilling liver homogenate into the antrum

These experiments proved that food in the gastric antrum produces a secretion of gastric juice by the fundus and body of the stomach The inhibitory effect of acidity in this region would represent an auto-regulating device which terminates the gastric phase of gastric secretion

[The results of Dragstedt s ingenious rearrangements of the dog s digestive tract are both revealing and perplexing One marvels that stimulation of the supposedly weak intestinal phase of gastric secretion causes concentrated acid (100 clinical units of free acid) to appear in the pouch At the same time the fact that acid stimulation of the antrum inhibits spontaneous but not vagally induced secretion is reconciled with difficulty to Dragstedt s opinion that interdigestive secretion such as night secretion is principally of nervous origin.—Ed.]

Quantitative Intragastric Determination of Acid Production in Normal and Diseased Stomachs is described by K H

of the jejunum to the main stomach secured gastrointestinal continuity The duodenum was divided the distal end infolded and closed and the proximal end brought through a stab wound in the abdominal wall as a cutaneous fistula A stainless steel canula was placed in the antrum

Irrigation of the antrum with physiologic salt solution caused no gastric secretion from the Heidenhain pouch and was used as a control procedure before and after each substance was tested The strongest secretory response was obtained by irrigation of the antrum with a liver homogenate having a pH of 6 3 When the homogenate had a pH of 5 no secretion was obtained from the Heidenhain pouch

EXPERIMENT 2—In the second animal isolated pouches of the body and fundus and of the antrum were prepared At first the esophagus was divided at the esophagogastric junction along with both vagus nerves The distal end of the esophagus was closed and the proximal end anastomosed to the jejunum. Later the antrum was separated from the main stomach pouch as in the first animal

When the antrum was perfused with physiologic salt solution the isolated denervated pouch of the body and fundus secreted no free HCl on 64 determinations Perfusion of the isolated antrum with a protein hydrolysate stimulated gastric secretion after two hours In three experiments perfusion of the antrum with a liver homogenate of a pH of 5 2 stimulated secretion However there was no secretory stimulation with a 3% solution of desiccated liver (pH 1 2) These experiments produced identical results in two other dogs similarly prepared

It is apparent that food substances can be acidified sufficiently so that stimulation of gastric secretion does not follow their application to the antral mucosa

EXPERIMENT 3—For the study of spontaneous gastric secretion the third and fourth animal were prepared with a gastric fistula and an isolated antrum pouch The antrum was separated from the main stomach as in the first animal A gastric fistula was created through the anterior wall of the main stomach The duodenum was transected and its proximal end brought to the surface as a cutaneous duodenal fistula The main stomach was anastomosed to the jejunum

These animals with an intact vagus nerve supply to the stomach frequently secreted acid gastric juice spontaneously while fasting Application of acid to the antrum promptly and completely inhibited gastric secretion in 15 experiments This inhibition seemed to be a function of hydrogen ion concentration and not specific for HCl

put is excessive In this type the stimulus is quantitatively normal

Histamine stimulates the acid secreting cells of the stomach directly It is possible to evoke from the stomach an apparent maximal output of acid by giving large doses of histamine while protecting the patient against the extragastric actions of histamine by administration of an anti

Secretion of Parietal Component (ml./45 minutes) by Normal Males and Patients with Duodenal Ulcer

	Normal	Patients with Duodenal Ulcer		
		No Stenosis	Mod Stenosis	Severe Stenosis
No persons	27	81	42	29
Mean basal secretion of parietal component	23 5	50 7	69 1	59 8
S E	±2 6	±3 8	±7 9	±6 9
Mean max. parietal response to histamine	86 0	135 3	165 1	160 4
S E.	±9 6	±7 1	±9 7	±10 1
Mean weight (kg)	60 8	58 5	59 0	53 0
S F	±1.8	±1 0	±1 1	±1 0
Mean age (years)	44 1	38.3	42 9	49 1
S E	±2.5	±1 0	±1 6	±1 4
Mean duration of symptoms (years)	—	13 1	15 0	17.2
S E	—	±0 9	±1 3	±1 6

S E = standard error of mean

histamine The authors used this as an index of the maximal secretory capacity of the gastric mucosa

Since the maximal secretory capacity in the duodenal ulcer group is greater than in the normal group (table) and since the threshold of parietal cell excitability is similar in the two groups it is to be expected that the ulcer group will always secrete more acid under standard conditions The mean percentage of maximal secretory power active during basal secretion in patients with duodenal ulcer is 38 9% and 33 7% in normal persons

Cox found that his male patients with duodenal ulcer had approximately 75% more parietal cells than normal subjects In the authors series maximal secretory capacity of the ulcer group was 72% greater than that of the nonulcer group These findings indicate an association between structure and function

Kimbel and H Kinzlmeier[2] (Univ of Erlangen) By this method hydrochloric acid secretion can be estimated with out considering the volume of gastric contents and dilution factors

METHOD—A double lumen tube was used One lumen equipped with an antimony electrode at the tip served to measure intragastric pH the reference electrode being placed in the mouth The second lumen was used for introducing alkali solutions With the patient lying on his left side the tube was passed into the gastric co ert which under these conditions pool in the greater curvature and te d to remain there for about two hours After a control period enough N/10 NaOH was introduced into the stomach to raise the pH to 5 The rate at which pH then returns to the control level affords an expression of gastric acid production

Studies in three patients showed that repeated injections of N/10 NaOH did not per se affect the rate of gastric e cretion A rebound phenomenon was thus not observed

In 15 subjects the rate of spontaneous hydrogen ion pro duction ranged between 3 11 and 11 24 mEq /hour The secretory rate achieved by giving caffeine or histamine to patients defined as having normal acidity did not exceed the spontaneous secretory rate in patients considered hy peracid A maximal rate of 15 5 mEq /hour was obtained in a hyperacid subject given histamine

Fluctuating secretory rates determined during the cour e of most tests indicated that the rate of hydrogen ion forma tion is not constant The rate of hydrogen ion formation in some patients is so rapid and prolonged that most antacids given in usual amounts are insufficient to sustain a pH of 5

[Continental investigators appear to be studying gastric secretion in creasingly by placing an electrode in the stomach and recording intra gastric pH continuously The technic here described depends a great deal on the assumption that gastric contents will not leave the stomach in ap preciab e amounts when the patient is lying on his left side—Ed.]

Nature of Gastric Hypersecretion of Acid in Patients with Duodenal Ulcer J N Hunt and A W Kay[3] state that gastric hypersecretion may be one of two classes In one maximal secretory capacity of the mucosa is normal but the proportion at work is increased Here it may be as sumed that there is an increase in stimulation of the parietal cells In the other maximal secretory capacity is abnormal ly high so that although the proportion of capacity which is actively engaged in secretion is normal the resulting out

(2) G t oente log 81 193 206 1954
(3) Brit M J 2 1444 1446 Dec 18 1954

motility began After 10 mg pathilon® intravenously all motor activity of the duodenum ceased He experienced slight relief after which the pain increased. Duodenal pH fluctuated between 1 31 and 1 40 When HCl was discontinued and normal saline given duodenal pH gradually rose to 3 01 and pain disappeared

CASE 3 — Man 47 had gastric and duodenal motor activity After introduction of N/10 HCl for 10 minutes duodenal pH dropped to 1 55 and ulcer pain immediately began Duodenal motility continued unchanged and gastric activity was reduced After 30 mg probanthine® intravenously duodenal activity ceased but pain persisted Because of severity of the pain the HCl drip was stopped After 30 cc of an antacid duodenal pH reached 6 02 and pain subsided

Intraduodenal administration of N/10 HCl invariably abolished gastric motility When duodenal pH dropped below 1 98 persistent burning pain not abolished by anticholinergic drugs developed in four of seven patients Onset of ulcer pain was not associated with change in duodenal motility

Effects of Smoking Tobacco on Gastric Acidity and Motility of Hospital Controls and Patients with Peptic Ulcer F Steigmann R H Dolehide and L Kaminski[5] (Chicago) studied the effect of smoking standard and filtered cigaret on gastric acidity and motility in 44 hospital controls and 54 peptic ulcer patients

PROCEDURE — Fasting patients were intubated with a Levin tube and gastric contents aspirated twice at 10 minute intervals After the second aspiration the patients were given a cigaret and aspirations were continued every 10 minutes for another six aspirations The samples were tested for free and total acidity The same procedure was continued for two mornings with the patient smoking a different type of cigaret each time

For motility studies a Miller Abbott tube with an attached balloon of about 50 cc capacity was passed into the stomach and placed in the antrum After a control period of 30 minutes the patient was given a cigaret and the beginning and the end of the smoking period were marked on the kymograph paper After this smoking period a second control period of 30 minutes was started Tracings of the fundus motility were made in a similar way except that a balloon of about 150 200 cc capacity was used Graphs were interpreted according to the height of each wave

A definite increase in gastric acidity followed the smoking of a standard cigaret in 50% of the hospital controls and in less than 25% smoking a filter type cigaret Of the ulcer patients over 90% showed a rise in gastric acidity with an

(5) Am J Gastroent 22 399 409 November 1954

The raised maximal secretory capacity for acid in patients with duodenal ulcer in whom stenosis develops is probably due to work hyperplasia of the parietal cells There seems to be no need to postulate an increase in excitation bearing on the parietal cells in patients with duodenal ulcer during basal secretion It is also possible that the vagus enjoys no direct long term control over the gastric mucosa at all but that the withdrawal of cephalic excitation on vagectomy results in a parietal diffuse hypoplasia which manifests itself in a lowered response to histamine

[*It is fashionable among gastroenterologic circles to belittle the significance of gastric acidity in peptic disorders Seemingly it has been investigated to death and people are tired of it Yet as this and the subsequent four articles show gastric acidity is not readily dismissed it remains a handy investigative tool and many old ideas can bear reinvestigation In this study Hunt and Kay resoundingly deny the beliefs that the stomachs of the normal person and the duodenal ulcer patient respond similarly to maximal stimulation and that the difference between the two lies chiefly in the increased stimulation to which the ulcer patient's stomach is exposed*—Ed]

Relationship of Ulcer Pain to pH and Motility of Stomach and Duodenum was investigated by Edward R Woodward and Herbert Schapiro[4]

METHOD—*The study patients had active but uncomplicated duodenal ulcers A triple lumen tube was passed under fluoroscopic control into the duodenum one lumen was used for inflating a balloon which recorded duodenal motility another for periodic aspiration of duodenal contents and the third for administration of N/10 HCl A double lumen tube was then introduced into the pyloric antrum under fluoroscopic control for recording gastric motility and aspiration of gastric contents*

In a pilot study it was found necessary to introduce N/10 HCl into the duodenum at 180 drops/minute to reduce pH ulcer pain did not occur until duodenal pH fell to 1 65 The findings are well illustrated in the following cases

CASE 1—*Man 57 had spontaneous ulcer pain initially Duodenal pH was 4 80 and gastric and duodenal activity was present With administration of N/10 HCl into the duodenum duodenal pH dropped to 1 88 and ulcer pain was intensified Duodenal motility continued unchanged gastric motility ceased Within two minutes after 4 mg antrenyl® was given intravenously duoedenal motor activity ceased for the duration of the study However duodenal pH remained between 1 30 and 1 62 and pain persisted*

CASE 2—*Man 31 had only gastric motor activity After introduction of N/10 HCl duodenal pH dropped to 1 76 and simultaneously he experienced ulcer pain Gastric activity ceased and duodenal*

(4) Proc Soc Exper Biol & Med 86 504 06 July 1954

motility began After 10 mg pathilon® intravenously all motor activity of the duodenum ceased. He experienced slight relief after which the pain increased Duodenal pH fluctuated between 1 31 and 1 40 When HCl was di continued and normal saline given duodenal pH gradually rose to 3 01 and pain disappeared

CASE 3—Man 47 had gastric and duodenal motor activity After introduction of N/10 HCl for 10 minutes duodenal pH dropped to 1.55 and ulcer pain immediately began Duodenal motility continued unchanged and gastric activity was reduced After 30 mg probanthine® intravenously duodenal activity ceased but pain persisted Because of severity of the pain the HCl drip was stopped. After 30 cc of an antacid duodenal pH reached 6 02 and pain subsided

Intraduodenal administration of N/10 HCl invariably abolished gastric motility When duodenal pH dropped below 1 88 persistent burning pain not abolished by anticholinergic drugs developed in four of seven patients Onset of ulcer pain was not associated with change in duodenal motility

Effects of Smoking Tobacco on Gastric Acidity and Motility of Hospital Controls and Patients with Peptic Ulcer F Steigmann R H Dolehide and L Kaminski (Chicago) studied the effect of smoking standard and filtered cigarets on gastric acidity and motility in 44 hospital controls and 54 peptic ulcer patients

PROCEDURE.—Fasting patients were intubated with a Levin tube and gastric contents aspirated twice at 10 minute intervals After the second aspiration the patients were given a cigaret and aspirations were continued every 10 minutes for another six aspirations The samples were tested for free and total acidity The same procedure was continued for two mornings with the patient smoking a different type of cigaret each time

For motility studies a Miller Abbott tube with an attached balloon of about 50 cc capacity was passed into the stomach and placed in the antrum After a control period of 30 minutes the patient was given a cigaret and the beginning and the end of the smoking period were marked on the kymograph paper After this smoking period a econd control period of 30 minutes wa started Tracings of the fundus motility were made in a similar way except that a balloon of about 150 200 cc capacity was used Graphs were interpreted according to the height of each wave

A definite increase in ga tric acidity followed the smoking of a standard cigaret in 50% of the hospital controls and in less than 25% smoking a filter type cigaret Of the ulcer patients over 90% showed a rise in gastric acidity with an

(5) Am J G t oent rol. 22 399 409 Novembe 1954

ordinary cigaret as compared with about 60% with a filtered cigaret (Fig 82) The rise in acidity with an ordinary cigaret was in the higher ranges and in the lower ranges with a filtered cigaret

Results of 6 fundic and 10 antral motility studies were somewhat at variance Smoking an ordinary cigaret de-

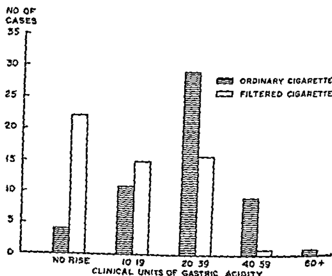


Fig 8 —Changes in g st acidity f llow ng smok ng of rd nary nd filt ed c g ret n pept c ul e p t ents (Courtesy of St gmann F et al Am J G tro-enter 1 22 399-409 No ember 1954)

creased antral motility more often than smoking a filtered cigaret but in most tests motility remained unchanged.

Effect of Tea on Gastric Secretions and Motility was studied by C Wilmer Wirts Martin E Rehfuss William J Snape and Paul C Swenson[6] (Jefferson Med College) Tea was prepared by steeping one bag containing 2 3 Gm tea in a cup of boiling water for three minutes It yielded about 45 mg caffeine/cup Throughout the study 10 Gm sugar was added to every 300 cc tea or water

To determine the effect of tea alone on gastric secretion and motility 12 subjects with duodenal ulcers in remission were given two cups of hot tea through a gastric tube after the fasting residue was tested for volume bile

(6) J A M A 155 725 7 9 Jun 19 1954

content pH and free acid Samples were similarly tested at 30 60 90 and 120 minutes Except for a small sample retained for chemical studies after each 30 minute period the gastric aspirate was reinjected into the stomach The same subjects were then studied with the hot tea replaced by an equal amount of hot water There was little difference in pH but free acid was somewhat higher and pepsin values somewhat less after tea than after water The bulk of both materials left the stomach at 30 minutes

After the fasting gastric residue was tested for volume bile pH pepsin and trypsin 250 cc of 40% emulsified olive oil was given with two cups of hot tea to 20 subjects The stomach was emptied at half hour intervals for two hours and after being measured the material was returned to the stomach except for a small sample The test was repeated on a different day with hot water and 12 subjects had similar studies with iced tea and iced water No significant difference was noted in pH free acid and pepsin between the tea and water but emptying time was shorter with tea than with water and with cold than with hot beverages

A barium meal and 250 cc of 40% emulsified olive oil and 300 cc hot or iced tea (or water) were given through a gastric tube to 16 subjects After the tube was withdrawn the subjects were observed fluoroscopically at intervals until complete emptying of the stomach Average emptying time in minutes was hot tea 266 hot water 327 iced tea 193 and iced water 250

It appears that tea taken in average amounts with sugar is not a potent gastric secretagogue in the fasting or postprandial state Tea like water taken in fasting state does not remain in the stomach long enough to have a profound effect on gastric secretions

It is probably becau e tannin is erroneously considered synonymous with tannic acid that large amounts of tea are thought to have a deleterious effect on digestion by precipitating proteins and albuminoses and thereby decreasing absorption and irritating the gastric mucosa Actually tea may aid digestion and relieve postprandial distress for the more rapid gastric emptying induced by tea may be associated with increased motility of the small intestine and

with flow of biliary pancreatic and intestinal juices In average amounts tea is not contraindicated in treatment of most gastrointestinal conditions

[These observations may be criticized on the grounds that the effects measured were not those of pure tea but of tea mixed with other foods. From the viewpoint of pure pharmacology this criticism is justified, but from the viewpoint of the clinician whose patients rarely consume food substances in pure and isolated form these studies may be highly significant The conclusion however that tea which is shown to stimulate gastric motility need not be contraindicated in the treatment of most gastrointestinal conditions may be questioned by some especially by those who feel that the pathogenesis and symptoms of duodenal ulcer are closely related to excess gastroduodenal motor function —Ed]

Stress and Gastric Secretion in Man I Study of Mechanisms Involved in Insulin Hypoglycemia Harry Shay and David C H Sun[7] (Temple Univ) studied the gastric secretory effect of insulin hypoglycemia in man to determine whether a double response curve to insulin hypoglycemia would be shown and if so whether the response could be resolved into its respective components

METHODS —In five patients with chronic duodenal ulcer each serving as his own control the following studies were made (1) Five hour basal secretion was studied on four different days in three (2) Effect of insulin hypoglycemia on gastric acid output was investigated in all 15 25 units regular insulin being given intravenously (3) Effect of insulin hypoglycemia and regitine® was studied in all five minutes after the start of an infusion containing 10 mg regitine® regular insulin was given intravenously (4) Effect of regitine® alone on basal secretion was studied in three (5) Effect of insulin hypoglycemia alone and with regitine® before and 15 days after bilateral vagotomy and subtotal gastrectomy was studied in one patient

Aspiration of gastric contents at a negative pressure of 30 in of water was continued throughout the test period

Figure 83 shows that secretion responding to insulin had gotten well under way after the first hour reached the first peak between 1½ and 2 hours the second between 3 and 3½ hours and perhaps a third one between 4 and 5 hours later When regitine® was used with insulin the first peak of the secretion curve remained but the late secretion was prevented A similar curve with early and late peaks of acid secretion was obtained in all five patients after insulin hypoglycemia One patient failed to show inhibition of the late secretory response when insulin and regitine® were ad-

(7) Am J M Sc 8 6 0-642 December 1954

ministered simultaneously Regitine® alone had no significant effect on basal gastric secretion

Studies on one patient before and after subtotal gastrectomy and bilateral vagotomy indicated that for the action of insulin hypoglycemia to produce the late curve or curves of gastric secretion neither intact vagi nor the gastrin mechanism is necessary In another patient the gastric acid

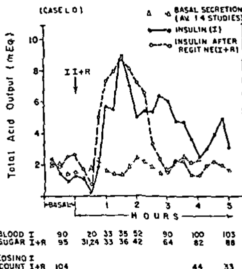


Fig 83—G t hyd ochlori ac d ponse t l n nd in l with g t ® w th blood g a d eo oph l ou t (Courtesy f Sh y H d S D C H Am J M Sc 228 630 64 Decembe 1954)

secretory response to insulin hypoglycemia was studied before and after bilateral total adrenalectomy It was found that at least one intact adrenal gland is necessary for the late phase of gastric secretion to appear after insulin hypoglycemia

As the stress stimulus supplied by insulin hypoglycemia in its effect on late curves of gastric secretion can be blocked in man as in the monkey by adrenergic blocking agents it is reasonable to suggest that epinephrine is liberated somewhere in the response to hypoglycemia and that

the epinephrine is important in release of ACTH to stimulate adrenal cortical hormone production and its effect on gastric secretion It is believed that an adrenal phase of gastric secretion should be considered in the peptic ulcer problem and that this phase is a significant part of the harmful somatic mechanisms activated by stress reactions

[Dismemberment of autonomic controls by surgical or pharmacologic means yields interesting information but in a sense is contrary to the very essence of autonomic function balance and counterbalance Thus the fact that both adrenergic and cholinergic stimulation are induced by stress is reasonable but that both act in the same direction i e are bad for the ulcer patient does not necessarily follow It is moreover quite definite that sympathectomy in man does not deter the formation of new or the recurrence of old ulcers—Eds]

Anterior Pituitary and Gastropepsinogen and Uropepsin Excretion M Saegesser[8] (Stanford Univ) investigated the relation between the anterior pituitary and gastric secretion by studying the effect of anterior pituitary extract on gastropepsinogen and uropepsin excretion Three dogs with a Heidenhain pouch two with the whole stomach isolated and two with antral resection and isolation of the fundus received a five day course of 1 cc /day of the extract

Whereas the gastropepsinogen excretion increased considerably in the Heidenhain pouch and the isolated whole stomach it was only slightly altered in the isolated fundus Thus the anterior pituitary seems to act on the antrum Though all animals received the same amount of anterior pituitary extract uropepsin excretion greatly increased in the dogs with the Heidenhain pouch and not in those with an isolated whole stomach As the stomach contents get freely into the jejunum in the former and not at all in the latter it follows that uropepsin does not enter the blood stream directly from the stomach cells but only through resorption of pepsinogen in the jejunum It was also found that the anterior pituitary does not act through the vagus or at least not only through it

In two dogs both adrenals were removed one eight days after the other They received 10 mg cortisone acetate from two days before removal of the second adrenal until the end of the test period and on the seventh and eighth days were given 1 cc of whole anterior pituitary extract The extract increased uropepsin excretion considerably a

(8) Schweiz med Wchnschr 84 1438 1440 D 25 1954

fact which suggests that the anterior pituitary regulates pepsinogen and uropepsin excretion in the dog directly through the stomach as well as indirectly through the ad renals

These conclusions hold only for dogs which normally excrete very little uropepsin (1 unit/hour) whereas its excretion in man is up to 5 15 units/hour

When injection of anterior pituitary extract was contin ued beyond five days gastric secretion acidity and pepsino gen production definitely decreased and mucus production increased especially in the isolated fundus

[If confirmed the results here reported will certainly knock sky high many of the theories concerning the relationship of the pituitary and the adrenal glands to gastric secretion It is apparent however that other investigators working with dogs are obtaining different results Un fortunately arguments concerning the validity of methods used to assay uropeps n in the urine and pepsinogen in the blood are threatening to convert the apparently solid pituitary adrenal gastric axis into a nebulous thread —Ed]

Experimental Observations on Psychosomatic Mech anisms I Gastrointestinal Disturbances J D French R W Porter E B Cavanaugh and R L Longmire[9] (Long Beach Calif) believing that chronic experimental stimu lation of the hypothalamic region should produce visceral disease implanted electrodes in the hypothalamus of 17 monkeys Ten received adequate daily stimulation for 30 74 days 3 received less than one stimulation a day and 4 which survived 6-14 days with poor stimulation records served as controls for early effects of operation Before stim ulation and three to five weeks later each animal had a gas tric analysis at which time aspirated stomach contents were tested for hydrochloric acid before and for four hours after excitation of the hypothalamus

Gross lesions in the upper gastrointestinal tract devel oped in 6 of the 10 test animals Four were sharply local ized in the pre and postpyloric region and two were gen eralized throughout the stomach Pathologic changes were edema atrophy and necrosis it is believed that alterations in the blood supply contributed greatly to the micropa thology

Antagonism irritability and restlessness developed two to four weeks after stimulation was begun in the three plac

(9) A M A. Arch. Neurol. & P ychiat. 72 267 281 September 1954

id monkeys in which lesions developed Immediate response to stimulation varied according to location of the electrode but generally the animals appeared bewildered occasionally sitting cowed in a corner or agitatedly pacing the cage Yawning was common as was barking and emotional reactions appeared as dilatation of the pupils ruffing of the hair and an attitude of challenging aggression or impelling escape

The pH values of gastric samples did not change until about five weeks after chronic stimulation was begun when the pH was depressed in animals with gastric lesions Body weight was unusually stable gain and loss being about evenly divided in monkeys with and those without lesions

Prolonged stimulation in or near the hypothalamus was the common etiologic factor in all lesions induced A single area mediating these deleterious influences on the stomach could not be assigned however as identical results were obtained when excitation was applied to the anterior or posterior areas Yet the entire hypothalamus cannot be considered equipotential in its ability to excite gastric lesions as stimulation of at least four points failed to elicit this response The possibility that different mechanisms emanating separately from excitation of either anterior or posterior hypothalamic nuclei were responsible for production of these lesions requires consideration

The location of effective stimulation sites in these animals suggests that structures conveying the mechanism necessary to excite these visceral changes course in the midline from preoptic to postmammillary regions and that this hypothalamic segment represents a funneling of diverse visceral influences from widespread cerebral and brain stem sources

To the gastroenterologist the reported changes in gastric acidity are not striking and for the most part in a pH range of moderate acidity The neurosurgeon also appears doubtful and wonders whether hypothalamic lesions can be created in animals or can develop in man without damage to other nervous tissue To wit

Ulceration and Malacia of Upper Alimentary Tract in Neurologic Disorders James MacD Watson and Martin G Netsky[1] (Montefiore Hosp New York) reaffirm the clinical significance of association between the central nervous system and the gastrointestinal tract

(1) A M A Arch Neu l & Psy hiat 72 426-439 Octo[ber]

They present 6 cases of combined neurologic and upper gastrointestinal disorders and review 38 similar cases from the literature All had complete autopsy reports and it could be safely assumed that the changes were genuinely ante mortem

Primary diagnoses and incidence were suppurative men ingitis 9 cases vascular accidents 10 tumor primary or metastatic 8 head injury and birth trauma 6 viral in fections encephalitis and poliomyelitis 4 asphyxia 3 mul tiple sclerosis 2 neonatal convulsions and malnutrition 1 gunshot wound 1 None was found to have evidence of the visceral circulatory stasis which Boles and Riggs con tended was the underlying condition in production of acute gastric ulcer of neurogenic origin

The clinical data analyzed do not contain instances of lesions so precisely localized as in experiments It was found that alimentary tract lesions can develop in patients with various neurologic disorders not necessarily postop erative patients with brain tumors

There were no neurologic diseases restricted to the hy pothalamus alone In all there was associated pathologic change in adjacent or distant regions of the brain Multiple metastases widespread changes associated with increased intracranial pressure and bilateral lesions secondary to cerebral arteriosclerosis were found in all cases in addi tion to primary lesions The hypothalamus was involved in only 30 cases

It is possible that neurologic mechanisms of higher cen ter (cortical subcortical) →hypothalamus →vagal nuclei or of higher center →vagal nuclei exist Such schemes alter the Cushing concept which did not admit of influence higher than the hypothalamus as a primary effector In this modi fied concept the cortex moderates the lower centers which escape when cortical centers or pathways are not function ing and exercise excessive parasympathetic effects on the viscera No physical proof of direct relation of neurologic and gastrointestinal disorders has however yet been es tablished

Acute Upper Alimentary Tract Ulceration and Hemor rhage Following Neurosurgical Operations In an analy sis of 7 000 neurosurgical records Richard A Davis Nich

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olas Wetzel and Loyal Davis[2] (Northwestern Univ) found 48 cases of acute upper gastrointestinal ulceration or hemorrhage during the postoperative period an incidence of 0 7% There were 24 instances in a series of 943 craniotomies 7 in 350 suboccipital craniectomies Progressive steps in the gastrointestinal tract complication were abrupt onset of hematemesis in a patient too ill to complain unrelenting gastrointestinal bleeding, shock, hyperthermia and death Eight patients had a history of gastrointestinal symptoms Thirty patients died In 15 of 24 in whom autopsy was done, ulceration was found or the cause of hemorrhage determined in 9 no gastrointestinal disease was demonstrated

There was no correlation between histologic character of the central nervous system lesions and occurrence of the gastrointestinal complication In 12 patients in whom sudden, massive hemorrhage after an initially smooth postoperative course was considered the direct cause of death nervous system lesions were frontal lobe glioblastoma (in 3) acoustic neurinoma and pituitary adenoma (2 each) and frontal lobe metastatic carcinoma, posterior fossa metastatic carcinoma cervical spinal cord arachnoiditis and no cerebellar pathology (1 each) Severe hematemesis occurred in absence of intracranial disease and after procedures such as laminectomy and trigeminal neurectomy

Cerebral pathology was anatomically extensive with the frontal lobe most often involved so that the physiologic effect of an isolated lesion was never obtained The infrequency with which the hypothalamus was involved (four cases) supports the conclusion that a lesion of the hypothalamus is not a requisite for gastrointestinal complications In addition experimental production of discrete anterior and posterior hypothalamic destructive lesions in 15 cats using the Clarke stereotaxic apparatus was not followed by hematemesis melena or pathologic evidence of gastrointestinal ulceration

The most plausible explanation appears to be the patient s metabolic response to the stress of surgery in which the central nervous system may or may not be involved by a pathologic process

(The fact that the hypothalamus is not invariably involved anatomically does not negate the possibility however that it is a crucial link in

(2) Su g Gynec. & Obst. 100 51 58 J nu ry 1955

mediating the effects of stress on the gastrointestinal tract Though dis agreeing sharply on some points the authors of the three previous articles appear to be unanimous that violent cortical stimuli can in some way exert peptic damage on the esophagus stomach and duodenum If this is the case, it would seem only logical that therapy of duodenal ulcer should be directed at the cerebral cortex As the next article shows it has taken some French physicians to put this concept into practice —Ed]

The Ulcer Problem has expanded beyond local disorder of the stomach and concerns the functioning of the entire organism P Frumusan and R Cattan[3] (Hopital St An toine Paris) consider gastroduodenal ulcer a gastric man ifestation of generalized illness Because the basic cause cannot be found in increased peptic activity of gastric juice study has been made of humoral vascular and neural factors which lay the groundwork for ulcer by damaging the gastric wall Humoral factors (hormones allergic re actions histamine acetylcholine) have not been shown to be of primary importance in ulcer formation The vascular factor is inextricably linked to neurogenic factors by way of the vasomotor nerves The neural factor in formation of ulcer acts not only by alterations in vascularity but by changes in secretion tonus and trophic condition of the stomach

The authors corticovisceral hypothesis is that ulcer re sults from a disturbance of corticogastric dynamics pro ducing hypersecretion muscular spasm and spastic vascu lar occlusion Disturbances may result from such external factors as emotions and conflicts or from internal ones (gastritis appendicitis colitis cholecystitis) The ulcer forms by autodigestion of an ischemic area but is merely a local expression of a generalized disorder Treatment may be directed against cortical dysfunction neural pathways (atropinization) vascular disorders or by treating the stomach locally

In three severe cases of ulcer which resisted all usual forms of treatment procaine was injected in the white mat ter of the frontal lobes as for intractable pain of cancer This procedure interrupts the pathways between the ante rior and dorsomedial nuclei of the hypothalamus and the prefrontal grey matter The injection is done with a stere otaxic instrument under x ray control One patient 74 had

(3) P méd. 63 398-401 M 16 1955

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(2) S rg Gynec & Obst. 100 51 58 J nuary 1955

output of hydrochloric acid was reduced by 50% or more and in 5 anacidity persisted during therapy In eight patients in whom maximal gastric secretion was induced and maintained by histalog the effect of pamine® intramuscularly was not impressive the volume and free acid decreased briefly in five and anacidity of short duration occurred in one patient

Pamine® was given orally in 5 mg tablets two to four times daily to 88 patients with peptic ulcer Clinical response was good in 62 Two patients have been without recurrence of ulcer for the first time in 10 and 15 years Recently however ulcers have recurred in several patients during therapy Side effects reported by 42 of the 62 patients included mouth dryness blurring of vision and constipation 7 noted delay in urination

Oral therapy was also tried in 37 patients with gastrointestinal disease other than peptic ulcer Diarrhea decreased and relief from cramping abdominal pain was noted in 11 of 16 with functional gastrointestinal disorders in 7 of 10 with regional enteritis and in 4 of 7 with severe ulcerative colitis Pamine® was ineffective in one patient with chronic recurrent pancreatitis Side effects were noted by 25 of the 37 in 11 the drug was discontinued

Pamine® appears to be a useful adjunct in treatment of peptic ulcer and other gastrointestinal disorders It is much less effective after intragastric or intraduodenal administration than after intramuscular injection the effective intragastric dose being about 500 times larger than the effective intramuscular dose Side effects in general are less severe than with banthine® and more pronounced than with prantal® these two compounds are less potent oral antisecretory agents than pamine® The ideal agent i e one that completely suppresses hydrochloric acid output for long periods without unpleasant side effects has not been developed

Observations on Diagnosis Treatment and Course of Gastric Ulcer Evaluation of Gastric Irradiation as Adjunct in Medical Treatment Erwin Levin Walter L Palmer and Joseph B Kirsner[5] (Univ of Chicago) treated 121

(5) J A M A 156 1383 1389 Dec 11 1954

a high gastric ulcer refractory to all therapy but was too sick to have subtotal gastrectomy Pain disappeared the day after procaine was injected, and there was x ray evidence of complete cure without additional treatment in two months A second patient had massive repeated intestinal hemorrhages from a duodenal ulcer which resisted therapy Hemorrhages were immediately stopped by procaine injections Gastrectomy could not be done in a third patient because of severe progressive bilateral pulmonary tuberculosis Procaine injections in the frontal lobes produced immediate functional cure

Pamine® Bromide Gastric Antisecretory Effects and Therapeutic Usefulness in Peptic Ulcer and Other Gastrointestinal Disorders Joseph B Kirsner Erwin Levin and Walter L Palmer[4] studied the effects on basal gastric secretion of pamine® given intramuscularly injected into the stomach or duodenum and given orally over a long period Also investigated were the effects of intramuscular doses on gastric secretion continuously stimulated by a histamine analogue and the clinical effects in ulcer patients

A single intramuscular dose of 0 014 1 4 mg completely suppressed output of hydrochloric acid in 25 of 47 patients in 10 secretion was inhibited for more than three hours Side effects mild with doses of 0 039 mg increased in severity in proportion to dosage

When 2 5 25 mg was given intragastrically pamine® produced anacidity in 22 of 57 patients Intraduodenal instillation of 10 20 mg inhibited gastric secretion completely in two of six patients Side effects were reported by 32 of these 63 patients but were mild with doses of less than 15 mg Single oral doses of 5 or 10 mg suppressed gastric secretion for 30 135 minutes in 3 of 10 patients In comparison, oral doses of 0 16 2 24 mg scopolamine hydrobromide, a chemically related substance produced anacidity lasting 105 165 minutes in 5 of 15 patients Drowsiness developed with 0 64 mg and increased in proportion to dosage Drowsiness was not reported by patients receiving pamine®

Fasting gastric secretion was measured at intervals during prolonged oral intake of pamine® in 15 patients In 13

(4) Gastroenterology 6 85 867 June 1954

to irradiation Although atrophy of the gastric mucosa de veloped in a number of patients at least temporarily macro cytic anemia was not observed nor did permanent digestive di turbances develop Seven patients died of carcinoma 1 of recurrent ulcer with acute perforation 13 years later and 17 of various other causes

[Those who like to consider duodenal and gastric ulcer as separate diseases have emphasized so insistently that gastric ulcer is accompanied by low acidity that medical attempts to control acidity in the treatment of gastric ulcer are often half hearted This work should show the error of this practice the control of gastric acidity is just as important for the control of gastric as for duodenal ulcer In evaluating the results achieved by Levin and his associates however it does not appear that the long term success of radiation therapy of gastric ulcer is any greater than that achieved by conventional medical management —Ed]

Effect of Prolonged Administration of Large Doses of Sodium Bicarbonate in Man was studied by G M T van Goidsenhoven O V Gray A V Price and P H Sanderson[6] (St Mary s Hosp London) Eight female and 25 male patients with peptic ulcer received a daily dose of sodium bicarbonate dissolved in 3 L milk and administered through a gastric tube for three weeks In addition most of them were given as much of a modified Meulengracht diet as they wished Doses up to 140 Gm sodium bicarbonate daily were well tolerated by nearly all patients Diarrhea was noted in one patient but stopped when alkali and milk were discontinued A few had constipation One had hematuria for three days while receiving 40 Gm sodium bicarbonate daily No cause for this was found

In all patients well marked alkalosis developed with increases in plasma CO_2 and pH Blood urea increased from 37 to 40 6 mg /100 ml the slight increase probably reflecting the high protein intake Clearance of inulin and endogenous creatinine indicated that the glomerular filtration rate is increased rather than impaired when sodium bicarbonate is given in large doses Balance studies revealed that the subjects retained large amount of sodium without ill effects most of it being accommodated in a greatly ex panded extracellular space If this is true amounts of chloride must enter the extracellular sources within the body presumably cells

Patients whose glomerular filtration rate is

(6) Cl Sc 13 383-401 A gu t, 1954

gastric ulcer patients with x rays to the body and fundus of the stomach in addition to the routine medical program to reduce acid gastric secretion Total depth dose was 1 100 2 930 r After discharge from the hospital the patients were observed frequently and adequate follow up was obtained on all but one

The diagnosis of benign ulcer was proved erroneous with cancer developing in five patients (4 1%) one of whom lived 3 years and another 4½ years after therapy In 20% who had atypical symptoms no definite food pain relation was noted

In this series acid gastric juice however small in quantity was indispensable for production and recurrence of chronic gastric ulcer Any procedure eliminating the acid entirely will therefore heal the ulcer and prevent its recurrence In 41 patients radiation induced achlorhydria lasted from 3 weeks to 13 years The ulcer healed completely in all but one *No ulcer recurred during the period of anacidity* The free acid decreased less than 50% in 20 patients In 2 of these the ulcer failed to heal and in 14 it recurred within two years Of 34 whose gastric acidity was reduced by 50% or more for at least 1 year only 5 had recurrences during the entire period of observation—*2 17 years*

Most ulcers healed in two to three months A few healed in less time *20% needed 120 days or more for complete* healing In the latter recurrences were frequent

As complications 42 patients had had hemorrhage and 8 previous acute perforation or obstruction Medical management including gastric irradiation reduced the incidence *of recurrent complications to 13 6% Only 4 of the 42 patients* who had had hemorrhage had recurrent bleeding The ulcer did not heal in six Patients with shorter histories had a somewhat lower recurrence rate Men seemed more resistant to treatment than women

Twelve of the 46 patients who had recurrent ulcer after their first course of radiation therapy received a second course *Of these* 10 had further trouble 6 then had surgery and 4 were continued on a medical program 1 of the 4 had no recurrence for at least five years

There were no complications such as malignant degeneration of the skin or injury to adjacent organs attributable

to irradiation Although atrophy of the gastric mucosa developed in a number of patients at least temporarily macrocytic anemia was not observed nor did permanent digestive disturbances develop Seven patients died of carcinoma 1 of recurrent ulcer with acute perforation 13 years later and 17 of various other causes

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Patients whose glomerular filtration rate is reduced by

(6) Clin. Sc 13 381-401 A gu t 1954

vomiting or hemorrhage are gravely handicapped as regards excretion of bicarbonate and small doses of alkali may cause a large rise in the plasma level This mechanism is partly responsible for the very high plasma bicarbonate figures occasionally seen in pyloric obstruction

It is suggested that alkalosis per se rarely if ever, causes renal or other damage and that the renal failure commonly seen in clinical alkalosis usually results not from alkalosis but from attendant dehydration and renal ischemia superimposed on previous kidney damage

[This study seems to indicate that the dangers of administering large doses of sodium bicarbonate for a period of three weeks to patients with *uncomplicated* peptic ulcer have probably been exaggerated On the other hand the possibility that a large amount of sodium bicarbonate taken over a period of years is deleterious to renal function is not excluded and the patient with an obstructed or otherwise complicated ulcer presents a different problem —Ed]

Clinical Trial of Robaden and Cabbage Juice in Treatment of Gastric Ulcer Richard Doll and Frank Pygott[7] (Central Middlesex Hosp London) treated their patients with fresh gastric ulcer with one of four regimens (1) robaden and cabbage juice (2) robaden alone (3) cabbage juice alone and (4) neither robaden nor cabbage juice Robaden is a preparation of gastric and intestinal tissue extracts which has been found to protect rats and guinea pigs against gastric ulcers Intramuscular injections of 1 ml robaden were given daily for the first 12 days and then 1 tablet orally three times a day until discharge Each patient received 1 L cabbage juice daily

All patients were kept in bed having only bathroom privileges for four weeks They were on a basic ulcer diet Half the patients in each treatment group were given 6 pt milk every 24 hours in a continuous intragastric drip for two weeks Progress was judged by the patient s symptoms and by measurement of the niche size

The course of gastric ulcer in 24 patients given cabbage juice and in a control group was similar during the month of treatment and in a subsequent two month follow up period In 32 patients given robaden by mouth for a month ulcers healed somewhat more rapidly than in the controls but the difference was not statistically significant and became even smaller after three months treatment

(7) Lancet 2 1200 1204 Dec 11 1954

Freedom from pain was however significantly greater in the robaden than in the control group

One hundred patients with gastric ulcer were given either robaden or placebo tablets After one year the two regimens appeared equally efficacious in alleviating symptoms or preventing relapses Robaden therefore does not seem to influence the healing of gastric ulcer

Significance of Local Vascular Changes in Bleeding Peptic Ulcer Calvin R MacKay[8] (U S P H S Hosp New Orleans) states that while vascular changes in the local ulcer area *are well described in textbooks their significance* particularly in event of erosion of the vessels by the ulcer has received little consideration The decision for surgery for bleeding peptic ulcer is usually based on the degree of *generalized arteriosclerosis* and the patient s age

Twenty five cases of bleeding peptic ulcer were studied with particular attention to vascular changes in the ulcer bed and immediate surrounding area and to the morphology of gastric and duodenal vessels remote from the ulcer area In the fatal cases arteriosclerosis or vascular disease was sought in other organs and tissues The cases fulfilled the following criteria (1) Severe bleeding had occurred based on a hematocrit reading of 25% or less (2) There was no history of hypertension or renal disease (3) No noteworthy generalized arteriosclerosis was demonstrable on clinical examination at surgery or at autopsy (4) There was no history of cardiac disease and none was evident at autopsy (5) Blood vessels in the ulcer area were demonstrable in microscopic sections

The changes affecting the vessels in the ulcer area were similar regardless of the patient s age and consisted of *proliferation of the intima* replacement of smooth muscle of the media by fibrous tissue and varying destruction of the elastica interna There was no arteriosclerosis of the vessels to the stomach or duodenum peripheral to the ulcer area Therefore the local vascular changes *in peptic ulcer* may be secondary to the inflammatory process which depends on the extent and duration of the ulcer regardless of the age of the patient or vascular pathology elsewhere

The pathologic physiology may be similar to arterioscle

(8) S g ry 35 724 733 M y 1954

rosis and in the case of erosion bleeding from the vessel is likely to be severe due to impaired contractility and poor coaptation of the intima Furthermore if obliterative endarteritis occurs it may be supposed that the resulting ischemia to the area may further delay healing of the ulcer, further scarring and make recurrences more likely

Body Weight after Gastrectomy Anthony Baron[9] (St George's Hosp London) studied body weight expressed as percentage of standard weight, of 285 patients before and after gastrectomy for peptic ulcer Gastrojejunal anastomosis was performed on 225 and a Billroth I operation on 60 Five day fat balance studies were carried out on 9 patients immediately before and one month after gastrectomy on 5 immediately before and one month after surgery other than gastrectomy and on 11 one year after gastrectomy (of these 5 had lost 20% or more of standard weight and 6 had maintained or gained weight) Daily fat intake during the balance period was 50 Gm Fecal fat was estimated by the Soxhlet method Twelve patients weighing 80 90% of standard before operation received nasal tube drip feeding of a high calorie high protein mixture starting on the third postoperative day if good bowel sounds were present

Postoperatively weight loss occurred in 25 30% of the patients being the greatest in the higher weight groups In one group studied at 2 6 and 12 months almost all weight loss occurred in the first two months (Fig 84) Average daily intake of 30 patients who had lost 10% of standard after gastrectomy was 2 800 calories at one year and much less in the first two months Diminished fat absorption follows gastrectomy but the drop is usually small (average 4%) After other operations a 3% decrease was found in two cases but scarcely any change in the other three Both dietary calorie intake and fat absorption are related to weight and failure to gain is most pronounced when both are impaired The impression is that calorie intake is the more important The weight gain of the 12 tube fed patients proved that postoperative weight loss can be largely prevented by high nitrogen high calorie intake

Patients complaining of weight loss include (1) those who failed to reach some arbitrary weight which they con

(9) Brit M J 2 69 73 July 10 1954

sider proper but have no real weight loss (2) those who were overweight before surgery and afterward lost considerable weight but ended within 10% of the standard figure (3) those who were underweight before surgery and lost some afterward but stabilized their weight at about 80% of standard and had a good or fair clinical result and (4) a group remaining between 60 and 80% of standard weight after operation There were 69 group 4 patients in the series Thirty were in higher weight groups before

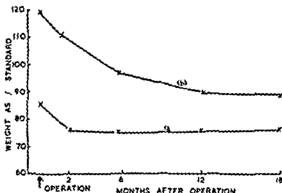


Fig 64—Weight loss patterns after gastrectomy av ge curve for 3 patients originally weighing 90-90% of standard b curve for originally overweight patient (Courtesy of Baron A Brit M J 69 3 July 10 1954)

surgery The others were in the 60-80% groups and failed to gain or lost weight afterward Most of the unsatisfactory clinical results occurred in group 4

[In this study the preoperative weight did not necessarily predict the postoperative weight On the other hand the clinical results support Zollinger's contention that the patient who is underweight before operation will be the one most apt to suffer from postoperative distress and fatigue In view of the high caloric content of the gastric or jejunal feeding administered to the 12 patients it is surprising that only 2 had diarrhea and distention Such side effects might well interfere with attempts to feed the early postoperative patient intensively—Ed.]

Potentialities of Electrogastrograph which depends essentially on d c amplification for success are discussed by H S Morton[1] (McGill Univ) who describes the apparatus and clinical application

(1) Ann Roy Coll Surgeons England 15 3 1 373 December 1954

rosis and in the case of erosion bleeding from the vessel is likely to be severe due to impaired contractility and poor coaptation of the intima Furthermore, if obliterative endarteritis occurs it may be supposed that the resulting ischemia to the area may further delay healing of the ulcer further scarring and make recurrences more likely

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(9) B r M J 2 69 73 J ly 10 1954

subsidence of symptoms recordings looked normal Active gastric ulcers gave regular recordings with moderate in crease in amplitude and faster frequencies superimposed In gastritis records fell in the normal range

Gastric cancer typically gave highly irregular records in most cases in both amplitude and rhythm In only 3 of 40 cases with proved cancer were the records not charac teristic In five diagnosed clinically and radiologically as cancer regular recordings were obtained at operation no malignancy was found

The EGG shows that drugs and certain emotions such

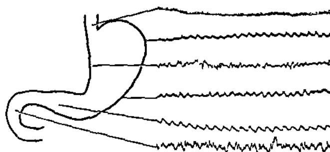


Fig 85—Norm l lect og t og m (Court y f M rt H S An Roy C ll S g E gl d 15 351 373 Dec mb 1954)

as hostility aggravation and anger influence the PD and motility of the stomach An emotional stimulus introduced during a normal recording caused a 10 mv change in PD level

In neurophysiologic investigations the island of Reil has been suggested as the center for speech taste smell and alimentation Its relation to alimentation is supported by EGG s showing well defined gastric motor responses to insular stimulation during an operation Ablation of the right insular cortex completely inhibited 3 cycle per minute waves

[Thirteen years have passed since Goodman reported his first attempts to diagnose gastric cancer by measuring intragastric potentials but development of the technic has been slow and retarded by technical diffi culties That h stam ne induced gastric secretion is attended by a change in gastric potential appears well established but the measurement of potentials produced by muscular activity rem ns subj ct to art fact

Silver silver chloride electrodes 1 mm in diameter and 4 mm long are used covered by a plastic cuff 2½ cm long filled with N/6 saline and with an absorbent cotton plug to act as a diffusion barrier The gastric electrode protected by 2 mm soft vinylite tubing is passed through the nose into the stomach under fluoroscopic control An identical reference electrode is applied on the skin in the right deltopectoral groove near the shoulder This site is least affected by sweating or drugs and is electrically the most stable

It is assumed that the electromotive force measured is produced in the stomach by the activity of the glands in the mucosa and by the action currents of the muscles Action potentials are the result of the depolarization of the cell membrane which follows cell stimulation and results in flow of ions from inside the cell outward Unlike an injury current depolarization ion flow is reversible and ions return into the cell on repolarization In measuring potentials with the EGG two factors have emerged (1) a potential difference (PD) level which is probably related to secretory activity and (2) small variations or a c components due to superimposed muscular activity

In the normal EGG the PD level is about zero varying ± 10 mv when the skin is used as reference The dominant frequency is 3 per minute with an amplitude of about 1 mv produced by gastric peristalsis The position of the gastric electrode modifies the pattern there is a negative slope from +10 mv at the cardia to −5 mv at the pylorus (Fig 85) The amplitude gradient is in the opposite direction Other frequencies such as respiratory effects can be identified and must be controlled A frequency of 6-15 per minute is usually observed in the small bowel but may occur in the stomach especially after vagotomy It is associated with rhythmic motion or churning Slower contractions about 1 per minute are due to specialized forms of peristalsis and still slower waves have been attributed to nausea

In addition to normal subjects measurements were made in patients with gastric symptoms but no evidence of gastric disease and in peptic ulcer patients In active duodenal ulcer increased and irregular activity was found After

tically significant Incidence of pernicious anemia among patients with gastric carcinoma was three times higher than in the normal population according with the finding of trebled incidence of gastric carcinoma in patients with pernicious anemia

No definite answer has been found regarding existence of an inherited tendency toward cancer in general It is concluded that exogenous factors—sex age race food in take gastric ulcer alcoholism occupation and pernicious anemia—cannot alone cause the greatly increased incidence of gastric carcinoma in relatives of gastric carcinoma pa tients but that the predisposition is inherited and that un known exogenous factors probably accelerate its develop ment Predisposition to gastric carcinoma does not appear to be associated with a general predisposition to cancer

Small Gastric Cancer Mandred W Comfort Howard K Gray Malcolm B Dockerty Robert P Gage George R Dornberger Jorge Solis Dean P Epperson and Robert A McNaughton[3] *(Mayo Clinic and Found) state that small* gastric cancers account for about a fourth of all gastric cancer treated by resection Of 226 small cancers divided according to size into four subgroups percentage differ ences of lymph node involvement were 11 1 24 5 44 8 and 58 7 respectively when the greatest diameters were 1 cm or less 1 1 2 cm 2 1 3 cm and 3 1 4 cm In 19 (8 4%) patients an active or healed duodenal ulcer was found

In small gastric cancer the ulcer and ulcer like symp toms predominate but in cancer of all sizes the nonulcer type of symptoms occurs more frequently Among gastric cancers with the greatest diameter 1 cm or less incidence of symptoms of the ulcer type (44 4%) and pseudoulcer type (50%) was much greater than that of the nonulcer type (5 6%) With increasing diameter the incidence changes to the reverse

Whereas 50% of those with an ulcer type history had had symptoms for more than five years 47 6% with a nonulcer type history had had symptoms less than six months Gastric secretory activity in small gastric cancer was below but nearer normal than in gastric cancer of all sizes

In this series x ray examinations indicated gastric can

(3) A M A A h I t Med 94 513 524 O t be 1954

since the technics used in man cannot prevent a relative shifting of the gastrointestinal wall with respect to the electrode Too little is known concerning the mechanisms responsible for physiologic and artifactitious changes in gastric potential to hold out much hope that the electrogastrograph can be used for diagnosis in the immediate future —Ed]

Etiology of Gastric Carcinoma Elucidated by Study of 302 Pedigrees Aage Videbaek and Johannes Mosbech[2] (Univ of Copenhagen) studied occurrence of cancer and pernicious anemia among relatives of 198 males and 104 females with gastric carcinoma selected without regard to age Diagnosis had been confirmed histologically in 79% by exploration or autopsy but without histologic examination in 12 and 8% respectively and by gastroscopy and x ray in 1% In 58% the carcinoma was at the pylorus or antrum in 37% in the body or upper part of the stomach and in 5% was diffuse or its origin unknown Of the 3 294 relatives 51% were alive without cancer 11% had had cancer and 38% had died without cancer

To ascertain the general incidence of cancer of the stomach and other sites 4 782 relatives of 390 healthy persons without particular symptoms (with careful exclusion of any showing signs of malignancy or blood disease) were studied Age distribution of the relatives was the same as in the clinical group Of the control relatives 36% were alive without cancer 7% had cancer and 56% had died without cancer

The number of cases of gastric cancer in the control series was only about half that expected from statistical calculations (a method involving important sources of error) whereas incidence of cancer of all other sites was the same or somewhat higher Gastric cancer appeared in 35% of the families of patients but in only 13% of the families of the controls Incidence of extragastric cancer was only slightly higher in the patient than in the control series Risk of gastric carcinoma among male and female relatives of gastric carcinoma patients is 29 and 21% respectively while corresponding risk values in the controls are only 7 and 5%

In relatives of patients with gastric carcinoma incidence of pernicious anemia was almost twice normal incidence but numbers involved were small and differences not statis

(2) Act med scandinav 149 137 159

his associates have now provided the evidence and delay in the surgical treatment of gastric ulcer will prove harder to justify particularly if the operative risks are small The risks however are not always inconsiderable The figures so courageously and honestly reported in the following article are much more significant for evaluating the average American s chances when he faces gastrectomy than the latest low mortality record achieved by a highly specialized surgical team whose services are available to only a few —Ed]

Gastric Resections—St Joseph s Hospital 1940 52 E Payne Palmer Jr[4] (Phoenix) reviewed 194 gastrectomies performed by 20 surgeons in this private hospital of a large community Preoperative diagnosis was duodenal ulcer in 112 gastric ulcer in 60 and adenocarcinoma in 14 patients Mortality rate was 9 03 with 18 deaths following gastric resection The fatalities were believed to be unavoidable in 10 patients 3 of whom had diffuse adenocarcinoma and were attributed to technical failure or surgical accident in 8 6 of whom had peritonitis caused by leakage of the duodenal stump The over all results are considered commendable and comparable to the records of other private hospitals

Gastritis A Revaluation Eddy D Palmer[5] (Walter Reed Gen l Hosp) summarizes experience based on clinical and gastroscopic surveys of 2 500 patients and on findings in 1 500 gastric mucosal biopsy specimens Control material included 265 specimens from 230 subjects The mucosa surrounding the biopsy site was studied endoscopically immediately after biopsy

In 73% of patients diagnosed gastroscopically as having chronic gastritis a better explanation (e g cholecystitis anxiety state) of the symptoms was eventually found It was also difficult to ascribe gastric bleeding to chronic gastritis in 45% of 49 patients with the gastroscopic diagnosis of hypertrophic gastritis and 79% of 14 with superficial gastritis bleeding was caused by acute superficial erosions which appeared unrelated causally to the chronic gastritis

The incidence of achlorhydria increases with age However no morphologic abnormalities were found in 30 patients over 60 Generalized alteration in mucosal structure is a consequence of disease not of aging

Although antral gastritis is a frequent radiologic diag

(4) A on M d 1 107 110 M h 1955
(5) M d e 33 199 90 S pt mb 1954

cer in 33 3% and suggested it in 36% whereas in 30 7% no features of cancer were detected When the diameter of the lesion was 1 cm or less x ray diagnosis was carcinoma in 11 1% with a diameter of 3 1-4 cm it was 46%

Over all hospital mortality for the 226 cases was 2 7% It was 1 8% for 219 patients with partial gastrectomy This is much less than for the 830 partial gastrectomies for gastric carcinoma of all sizes (6 4%) during the same period The

Fig 86—Survival rates (C t y f C mf t M W et al A M A Arch I t Med 94 513 524 October 1954)

risk of surgical removal of small gastric cancer was less than for gastric cancer in general

The five year survival rate following gastric resection for patients with small gastric cancers (44 7%) is about 40% greater than for patients with gastric cancer of all sizes (31 6%) It also is nearer the rate for the normal population The five year survival rate for this series varied with size of the lesion (Fig 86)

[One weakness in the argument that all gastric ulcers should be treated surgically for fear of malignancy has been this heretofore unanswered question if an early gastric cancer masquerading as a benign ulcer is removed surgically what is the evidence that the patient s life expectancy is better than that usually associated with surgically treated gastric cancer particularly if an ulcer operation without extensive resection of regional lymph nodes is used to remove the lesion? Comfort and

Studies on 34 men during severe alcoholism revealed acute exogenous gastritis characterized by patchy mucosal hyperemia erosions petechiae and purulent exudate The abnormality extended from neck to surface sparing the epithelium Nine of 11 patients had normal biopsy results after several days of abstinence Although alcoholism as a cause of chronic gastritis is not substantiated by clinical or pathologic evidence associated malnutrition and liver disease may be responsible for disease of the stomach In patients with hepatitis there was no correlation between incidence or type of gastritis and stage or severity of hepatitis Forty six of 55 biopsy specimens taken at gastroscopy were normal

Gastroscopy of 64 patients with prolapse of the antral mucosa revealed little gastritis and no disease suggesting trauma to the prolapsing segment Similarly although esophagoscopic and gastroscopic study of 100 patients with hiatus hernia showed mucosal venous engorgement to be common in the herniated segment no great incidence of chronic gastritis was observed

Surgery on the stomach is almost always followed by acute generalized gastritis with mucosal edema hyperemia and purulent exudate The foveolae showed tortuosity heavy epithelial staining and round cell infiltration Biopsy specimens taken 2 1 612 weeks after surgery showed gastritis in 47 of 84 patients Specimens revealed the same abnormalities whether removed weeks or years after surgery Vagotomy seemed to protect the mucosa somewhat

Although chronic hypertrophic gastritis has been often reported by gastroscopists the pathologist sees it infrequently In 52 patients with a gastroscopic diagnosis of chronic hypertrophic gastritis repeated examination revealed a marked changeability in the appearance of the stomach On biopsy 42 specimens from 33 patients were normal in all respects The gastroscopic picture of chronic hypertrophic gastritis is believed to be caused by hypertonicity of the muscular coats i e it is not gastritis at all but functional disease characterized by a tense stomach

Giant rugae should be differentiated from the rare giant hypertrophic gastritis The latter is caused by four different histopathologic reactions mucosal hyperplasia connective tissue septa producing large folds foveolar hyperplasia *with septal extensions and mixed forms Giant hypertro*

nosis gastritis as diagnosed endoscopically or by biopsy specimens exhibits no tendency to localize specifically in the antrum

Acute erosions chronic erosions and ulcers may be differentiated The acute erosion an apthous ulcer' a few millimeters in diameter forms and heals quickly and is caused by damage to and tissue dehiscence at the neck level of the gastric glands (Fig 87) Chronic erosions occur in scattered groups present umbilicated craters 4 5 mm in

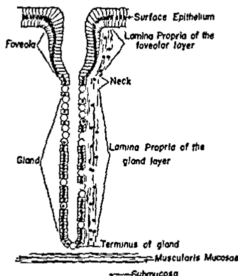


Fig 87 (C rt y f Palm E D M d c 33 199 290 S pt mbe 1954)

diameter extend part way down into the mucosal layer stimulate a local eosinophilic reaction and heal in days to weeks An ulcer involves the submucosa Erosions do not progress to ulcers

A prerequisite for diagnosis of gastritis is epithelial disease not round cell infiltration The cellular content of the lamina propria was however not increased in biopsy specimens of a healthy subject taken before and after a meal

The mucosa in acute staphylococcic gastritis showed local death and extrusion of cells in the neck region After 92 hours the histologic picture became normal suggesting that the condition has no tendency to becom ic

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phic gastritis therefore has no uniform histopathologic significance

The stomachs in 83 cases of chronic superficial gastritis were covered by opaque exudate The stomachs contained purulent material with pus cells mucus and desquamated surface epithelium All had patchy mucosal hyperemia—rarely large diffuse areas and never generalized hyperemia This picture tends to change slowly with time and occasionally leads to development of atrophic gastritis

Gastroscopic diagnosis of chronic atrophic gastritis is usually easy but at times especially in pernicious anemia the mucosa may appear normal even though histologic study shows atrophy Characteristics are muscular hypertrophy atrophied gland layer heavy cellular infiltrations and intestinal metaplasia In 70 patients with chronic atrophic gastritis associated abnormalities were 47 with histamine achlorhydria 14 with cancer and 5 with adenoma

Palmer classifies diffuse mucosal diseases of the stomach based mainly on the microscopic picture, as follows (1) acute degenerative gastritis (2) acute hemorrhagic gastritis (3) chronic degenerative gastritis with diffuse infiltration into the superficial lamina propria mostly by plasma cells and lymphocytes (4) chronic atrophic gastritis and (5) chronic hyperplastic gastritis frequently a further stage of chronic atrophic gastritis

[In this extensive and thoroughly documented review—in which the author looks critically not only at others but also at himself—the clinician may discover why the entity of gastritis is so confusing Palmer thoughtfully provides a figure herewith reproduced to make the text intelligible to the many of us who are frightened by the complexities of histologic nomenclature Schindler would probably challenge many of the conclusions since he feels that the vacuum tube biopsy techni does not provide adequate specimens —Ed]

Risks of Peroral Endoscopy are discussed by Eddy D Palmer[6] (Walter Reed Gen l Hosp) In certain patients the normal autonomic connections provide for potentially dangerous esophagocardiac and gastrocardiac reflexes In particularly sensitive persons the mere act of swallowing whether or not there be a tube in the gullet periodically leads to atrioventricular block Peroral endoscopy is more dangerous under general anesthesia than under buccal and pharyngeal anesthesia using pontocaine[6]

Toxic reactions to local anesthetics may be lessened by

(6) U S Armed Fo es M J 5 974 994 July 1954

premedication with barbiturates and by using the anesthetics as a gargle and not as a spray In prevention of such reactions a history suggesting sensitivity is more helpful than cutaneous or conjunctival tests A toxic reaction may start with a sneeze and proceed to bronchospasms massive pharyngeal edema or circulatory collapse Occasionally deep coma supervenes and respiration decreases as cyanosis trismus and clonic seizures develop Treatment includes use of sodium amobarbital intravenously A respirator should be at hand At Walter Reed Hospital only 14 local anesthetic reactions (without fatalities) occurred in 4 350 peroral endoscopies

In 25 077 gastroscopies in the literature the perforation rate was 0 108% and the fatality rate 0 032% Of the 27 perforations 22% occurred through the pharyngeal wall 41% through the esophagus (the most fearful) 33% through the stomach and 4% through the jejunum As judged by the perforation reports the Herman Taylor gastroscope is more dangerous than the Wolf Schindler design

Most esophagoscopic perforations occur proximal to the cricopharyngeal muscle leading to a rapidly descending infection Early signs are sore throat deep neck pain and fever They demand immediate drainage of the region A large proportion of reported esophageal perforations have occurred in women past 50 Though an occasional patient recovers on conservative medical treatment immediate thoracotomy and mediastinal drainage is the treatment of choice

Rare complications of gastroscopy are passage of air through the gastric wall without a demonstrable wound interstitial emphysema of the gastric wall and hematemesis In nearly all cases of gastroscopic perforation of the stomach treatment consists in gastric aspiration for five days antibiotic therapy adequate sedation and analgesia Laparotomy is more often harmful than helpful

Aortic aneurysm contraindicates endoscopy unless there be a foreign body in the esophagus Previous x ray of the esophagus is a legal necessity except in conditions requiring quick action such as massive upper gastrointestinal hemorrhage of unknown origin

[Sudden death apparently caused by a pontocaine® gargle has since been reported by Palmer —Ed]

Primary Diverticula of Duodenum John M Waugh and Edward V Johnston[7] (Mayo Clinic) state that autopsy studies have revealed diverticula in up to 14 5% of duodenal dissections whereas x ray surveys have disclosed an incidence of only 1 or 2% The higher figure is probably closer to an accurate estimate for the adult population

The authors reviewed 30 surgically treated cases of duodenal diverticulum In 20 of these, the diverticula were excised inverted or obliterated at the neck but in only 8 was the diverticulum the primary indication for operation Two postoperative deaths were due to complications of diverticular excision and one patient had a subhepatic abscess In exposing diverticula injury to the pancreas must be avoided as it may lead to acute pancreatitis

Primary diverticula cause no typical symptoms The most common complaint is abdominal distress in the epigastrium right upper quadrant or periumbilical region usually made worse or brought on by eating a large meal and relieved by vomiting or belching In four cases there was a history of melena and secondary anemia No ulcerative or bleeding lesions were found in any of the diverticula although a clot was present in a diverticulum of one patient

Follow up of seven patients who had surgery for their duodenal diverticula revealed that one had no further bleeding after obliteration of the diverticulum Another patient had recurrent bleeding from a gastric lesion Duodenal diverticula are seldom the source of upper gastrointestinal bleeding even when no other lesion is demonstrable Three patients continued to have the symptoms present before operation two others obtained complete relief

[In general more errors will be made by assuming that some duodenal diverticula cause symptoms than by assuming that all such diverticula are harmless —Ed]

(7) Ann. S rg 141 193 00 February 1955

Roentgen Findings in Strangulating Obstructions of Small Intestine are described by Harry Z Mellins and Leo G Rigler[8] (Univ of Minnesota) An obstruction is strangulating if in addition to a block in intestinal continuity there is evidence of compromise of the blood supply There are two groups of problem cases of obstruction (1) those in which strangulation is not revealed and signs of obstruction are also disguised and (2) those in which treatment should be nonoperative if possible and would be if it were certain that strangulation was not present The second group includes poor operative risks partial small intestine obstructions and inflammatory lesions with an obstructive component

Study of 334 small intestine obstructions revealed 34 of the strangulating type Of these 26 were studied by x

ROENTGEN FINDINGS IN 26 CASES OF STRANGULATING OBSTRUCTION

Closed loop		15
A Gas distended (coffee bean sign)	7	
B Fluid filled (pseudotumor sign)	8	
Fixation of loop		13
Loss of mucosal pattern		12
Absence of gas above obstruction		6
Lack of decompression of localized segment following suction		3
Presence of small amount of gas in colon		17

rays (table) In almost 60% a closed loop was demonstrable In three there were only the signs of simple obstruction and in one even mechanical obstruction could not be diagnosed

Certain x ray signs are strongly suggestive of strangulating obstructions and when present should lead to the diagnosis If the twisted loop is only partially closed it will be filled with gas or gas and fluid On the horizontal film gas will be seen in the two distended limbs of the loop The gas shadows will be separated by the apposed intestinal walls (Fig 88) the coffee bean sign If the loop is com

(8) Am J Roe tgen l 71 404 415 M b 1954

pletely closed there will be little or no gas and the loop will be seen as a rounded soft tissue density—the pseudo-tumor sign This sign is enhanced by presence of gas in the upper small intestine A third sign is fixation of a loop of intestine This is brought out by pictures taken in the erect supine and lateral decubitus positions Lack of move



F g 88.—Coff e be gn Ope t on ealed a g s-d ste d d, ca cerated loop ob tru ted at two po t by po t perat e dh s on b t stra g lat on had n t per ened (Court y f Mell H Z a d R gl r L. G Am J Roent gen 1 71 404-415 Ma ch 1954)

ment of the loop favors a diagnosis of closed loop obstruction A fourth sign is loss of the normal mucosal pattern within the closed loop or above it due to anoxia followed by loss of tone of the muscularis Additional signs of collateral value are absence of gas in small intestine in clinically suspected small intestine obstruction unusually large amounts of fluid in the lumen of the small intestine long fluid levels far beyond the usual size distention of an in

testinal segment far out of proportion to the remaining loops absence of decompression of a localized loop following suction siphonage and moderate amounts of gas in the colon despite the apparent evidences of small intestine obstruction Although some gas is often present in the colon there is no colic or rectal distention a fact tending to rule out paralytic ileus

Differentiation of simple from strangulating obstructions may be difficult if the patient is seen three to six hours after onset of symptoms Repeat examination in a few hours will probably indicate the proper diagnosis The usually lobulated outline of the pseudotumor shadow should differentiate strangulating obstructions from other pelvic masses

Malignant Argentaffinoma With Cyanosis and Pulmonary Stenosis In 1954 Thorson *et al* reported a series of cases of malignant argentaffinoma of the intestine with metastases in the liver a peculiar patchy cyanosis and transient vasodilatation of the skin pulmonary stenosis and tricuspid incompetence Diarrhea and peripheral edema were commonly present and in some instances there was ascites

J S Jenkins and P J A Butcher[9] (St Bartholomew s Hosp London) report two cases Both patients had long standing diarrhea and peripheral edema with ascites in one The vasomotor changes in the skin of one patient were so characteristic that their recognition should lead to a presumptive diagnosis of metastasizing argentaffinoma The other patient did not have widespread cyanosis but only a malar flush In this case there was clinical and autopsy evidence of pulmonary stenosis and tricuspid incompetence In both cases autopsy revealed an argentaffinoma of the intestine which had metastasized extensively—to the liver lymph nodes and in one case to the ovaries

It seems that widespread metastases are necessary for skin and cardiac lesions to develop since these have not been reported in cases in which the argentaffin tumor remained localized to the intestine

According to Thorson *et al* this syndrome probably results from an excessive secretion of 5 hydroxytryptamine by the tumor This substance also called enteramine has been

(9) La et 1 331 333 F b 12 1955

found in normal intestinal mucosa It is present in normal serum and blood platelets and because of its vasoconstrictor properties has been called serotonin

["Carcinoid heart disease not only is a fascinating entity but also hints at the latent humoral power enjoyed by the argentaffin (chromaffin) cells scattered throughout the muco a of the gastrointestinal tract. The normal function of 5 hydroxy tryptamine is still obscure and any excessive amounts formed by intestinal carcinoids apparently are inactivated by the liver the lung or both On the other hand 5 hydroxy tryptamine elaborated by carcinoid metastases in the liver or in organs drained by systemic veins (i e ovary) is responsible for (1) diarrhea (2) right sided cardiac lesions as here described and (3) increased urinary output of a derivative 5 hydroxy indolacetic acid Urinary analysis for this substance can be used as a test for metastasizing carcinoids —Ed]

Treatment of Celiac Disease with the Specific Carbohydrate Diet Report on 191 Additional Cases Sidney V Haas and Merrill P Haas[1] (New York) report on 191 patients with celiac disease treated since 1950 and followed with enough care and for a sufficient time to warrant evaluation of progress and outcome 127 other cases seen briefly, are not included

Treatment was the specific carbohydrate diet which eliminates food containing carbohydrate other than that found in fruits and to a lesser extent in vegetables and in protein milk From empiric evidence the authors believe that patients with celiac disease tolerate only monosaccharides and that polysaccharides (including disaccharides such as sucrose lactose and maltose) cause diarrhea

Vitamin supplements especially A and D are valuable but other agents such as opium kaolin and pectin are not Sulfonamides and antibiotics often stop diarrhea but the effect is transitory

Recent British and Dutch reports maintain that a substance in the gluten fraction of wheat flour produces the symptoms of celiac disease and that removal of wheat from the diet eliminates them However 33% of the authors patients had symptoms before solid foods were given They have observed continuing symptoms in patients on wheat free starch free diets unless other polysaccharides were also eliminated After recovery on the specific carbohydrate diet wheat can be used liberally without ill effects

(1) Am J Gastroenterol 23 344-360 Apr 1 1955

The criterion of successful treatment is perfect nutrition and health with complete cessation of diarrhea within 12 18 months regardless of what foods are used thereafter With the specific carbohydrate diet diarrhea was controlled with in one month in 38% of the 191 patients In some cases diarrhea may persist up to a year but prognosis is good if nutrition is improving The so called celiac crisis with severe dehydration and electrolyte imbalance was not seen in these patients

Behavior disturbances a prominent aspect of the illness improved with correction of the nutritional disorder Al though parents fear that rigid adherence to the diet may produce personality problems experience has shown that the personality pattern of the child is directly dependent on adherence to the diet If prohibited food is introduced the child will be irritable unhappy and poorly adjusted When the diet is carefully supervised he will be pleasant happy and tractable

Celiac disease has many aspects of a stress syndrome Regardless of the type of dietary management certain situ ations seem to be consistently associated with increased diarrhea The most common of these are infections pain (particularly in teething) unusual or excessive physical exertion and emotional irritations

[That the Haas diet sometimes relieves symptoms of celiac disease or sprue dramatically must be accepted but the frequency with which it achieves success or the degree to which it assures sustained improvement is uncertain Unfortunately Haas and Haas do not strengthen their case by dismissing from their report 127 cases seen so briefly that their consideration in a scientific report is unjustified —Ed]

Celiac Disease Is There a Natural Recovery? J W Ger rard C A C Ross R Astley J M French and J M Smel lie[2] (Univ of Birmingham) assessed the clinical and bio chemical recovery of 20 girls and 12 boys aged 4 19 who had been treated for celiac disease before 1949 and had not been treated with a gluten free diet No child was complete ly free from symptoms the most common being diarrhea (19 patients) Weights averaged 12 4% below normal and heights 7% Ossification was retarded in eight patients Fat balance studies in 11 children and stool examinations

(2) Q rt J M d. 24 23 32 J ry 1955

in 20 others demonstrated that these children were still losing more than twice as much fat in the stools as normal children Results of the oral glucose tolerance test were normal in only six patients Steatorrhea in older children is not always associated with diarrhea most of the stools of the older children were normal in color and consistency despite the high fat content Some degree of dilatation of the small intestine was present in 22 of 30 patients examined

This study demonstrates that celiac disease may persist for many years in children who have not been maintained on a diet free from wheat gluten A gluten free diet produces rapid improvement but it must be maintained to insure normal development and to prevent such complications as nutritional anemia rickets and tetany The observation that some adults with steatorrhea respond less favorably than children with celiac disease to a gluten free diet suggests that the disease process if allowed to persist may become irreversible

Because of the findings in untreated patients and the relapses and growth disturbance in children taken off the diet after disappearance of symptoms the authors believe that the diet should be maintained until active growth has ceased

Celiac Disease—What Is it? L Emmett Holt Jr[3] (New York Univ) defines idiopathic celiac disease as a state of malnutrition induced by a poorly understood chronic functional disorder of intestinal assimilation The characteristic pale bulky stools are due to an excess of unabsorbed fat their frothy character is due to carbohydrate fermentation and the patient s cranky disposition is attributable chiefly to the somatic disorder

The percentage of fat in the stools (and consequently stainable fat) is not a reliable measure of absorption It may be high or low in conditions of excellent absorption and may be low when much fat is being lost At present no simple clinical method for measuring fat absorption is available As valid statistical evidence is lacking, one should not conclude that starch intolerance represents mild or early celiac disease with specific therapeutic indications

(3) J Ped 46 369 379 Apr 1 1955

It is felt that the increased fecal loss caused by giving poorly tolerated food merely demonstrates rather than induces the intolerance Administration of a sizable fat supplement to celiac patients although it increased the loss of fecal fat brought about a substantial increase in the amount of fat absorbed Only favorable reactions were noted clinically

The explanation for the frothy stools in celiac disease appears to be that it takes little sugar to make a lot of gas Holt calculated that 1 Gm sugar is capable of forming 745 cc CO_2 The few bubbles of gas noticed in the stool represent amounts of sugar which are infinitesimal and which from the point of view of nutrition can be completely ignored.

Although Holt grants that allergy to wheat protein can produce celiac disease he finds it difficult to believe that it accounts for more than a small percentage of cases

Ever since the first descriptions of celiac disease appeared quite different and even opposite diets have been advocated They all appear to have produced excellent results which is not too surprising in a condition with a tendency to spontaneous improvement even though it is slow and punctuated by relapses Holt concludes that there is no need to exclude either fats or sugars from the diet

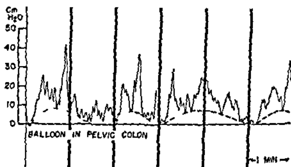
Normal and Some Abnormal Colonic Motor Patterns in Man are described by Charles F Code George R Wilkinson Jr and William G Sauer[4] (Mayo Clinic and Found) To record motor activity in the colon either balloons or pressure transducers have been used With the first method the record obtained describes pressure changes in the balloon produced by motor activity of the wall of a single bowel segment The tiny electrically operated transducer provides pinpoint detection of pressure changes in the bowel lumen Contractions insufficient to raise the pressure in the bowel would not be recorded or contractions in one segment accompanied by relaxation in adjoining segments might if the transducer lay between them be undetected

Waves recorded throughout the gastrointestinal tract are classified as types I II and III Type I waves most readily detected in balloon tracings are small and simple In the

(4) Ann N w York Acad Sc 58 (Art 4) 317 335 1954

colon they are uncommon and often difficult to distinguish from respiratory effects When rhythmic the rate in the pelvic colon is 13/minute in the descending colon it may be about half this figure The function of these waves is unknown

Type II waves are simple and of greater duration and amplitude than type I waves Presumably they cause the haustra seen in x rays Their function is mixing rather than propelling In the pelvic colon where they are satisfactorily detected by both transducer and balloon they last 1/3 ½ minute The pressure they produce is least in the lower



F g 89 —Type III wa es (d tted line) rd d fter i g i on of food f om pel olon of rmal per on (Cou t sy f Cod C F et l An N w York Acad Sc 58 (art 4) 317 335 1954 fr m Sp gg E A et al G t oent r logy 19 4 0 1951)

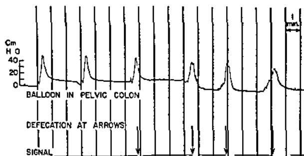
colon When rhythmic their frequency is 2/minute In normal persons bursts of type II waves constitute 90% of the colonic activity

Type III waves (Fig 89) are complex composed of a change in base line pressure or tonus with superimposed type I or II waves or both The base line changes are usually of low amplitude but of long duration These waves probably aid absorption by increasing intralumen pressure

Patients with ulcerative colitis produce waves (type IV) that are large and simple (Fig 90) They usually present a steep or rapid rise in pressure which may be considerable and a more prolonged decline The waves are propulsive and occur simultaneously, or almost so in both balloons of a tandem system They represent simultaneous not peristal

tic contractions of the bowel over a distance of 12 14 cm or more When the waves are rhythmic the maximal rate is 1/two minutes This has been recorded quite regularly after neostigmine administration

In a study of the pelvic colon in 10 fasting normal sub jects some activity was found about a third of the time Type I waves were present only about 1% of the time and type III about 2% Most of the activity was due to type II waves No type IV waves were seen In normal persons



F g 90—Typ IV w ord d ft g t on f food f m pel olon f l t lt p t t (C rt y f C d C F t l A N w York Acad S 58 (rt 4) 317 335 1954 f om Sp gg E A t l G t ent logy 19 480 1951)

activity of the pelvic colon and of the gastric antrum are somewhat similar

In 10 ulcerative colitis patients over all motility of the pelvic colon was decreased Type II and III waves were reduced or replaced by type IV waves These patients do not need antispasmodic or cholinergic blocking agents since their over all colonic motility is already diminished Ther apy ideally requires a drug that would increase the normal type II and III mixing and absorbing waves but would decrease the frequency of the dangerous type IV waves

Comparative Potency of Newer Anticholinergic Drugs in Man As Determined by Sigmoid Motility Technic Marvin H Sleisenger Mark Eisenbud and Thomas P Almy[5] (New York Hosp—Cornell Med Center) tested the anticholin ergic activity of 16 synthetic compounds by the kymograph ic recording of phasic contractions of the sigmoid in 102

(5) G t oent logy 27 829 837 D mber 1954

patients with no organic colonic disease Patients were prepared by an 8 16 hour fast and one or two enemas A 15 30 minute control tracing was obtained before any drug was administered A positive effect was defined as complete abolition of spontaneous contractions for at least 15 minutes

According to the over all percentage of positive effects of all types the following drugs were ineffective RO 2 3202 TBEMS Ciba E 1459 bellafoline Nu 2172 Lilly 09301 Variably effective were homatropine methylbromide panparnit® bentyl® Sch 1667 citrate and WIN 5766 Prantal® SC 3183 antrenyl® Lilly 14045 and probanthine® were frequently effective

The drugs tested had anticholinergic potency on lower animals and from these results the estimated human dose had been calculated Yet most of the drugs had little or no effect on the resting motility of the sigmoid colon even if given in several instances in doses up to three times those recommended Even though several compounds received too few trials in too narrow a range of dosage the findings indicate that calculation of human dosage based on animal experiments is inadequate

All compounds in the frequently effective group are quaternary amines and all but one combine ganglionic blocking with an atropine like action on postganglionic cholinergic nerve endings When given in effective amounts all had atropine like side effects When the dosage was lowered to decrease toxic reactions the colonic effect was also decreased The compounds with no side effects had little or no colonic effect It therefore seems unlikely that with the agents available potent anticholinergic effects on the bowel can be had without minor toxic effects

Although an anticholinergic drug may inhibit segmental movements it also markedly reduces activity of the proximal colon where peristaltic movements arise Hence anticholinergics have little value for constipation In view of the complexities of colonic motor disturbances an all purpose antispasmodic drug is not likely to be found A better knowledge of the mechanisms of intestinal motor disturbances should suggest which type of pharmacologic activity would be desirable in therapy

[The point emphasized both here and by Kirsner *et al* (see p 496) bears repeating the dose of anticholinergic necessary to produce objectively discernible motor or secretory effects is a dose sufficiently large to produce side effects —Ed.]

Autonomic Nervous System Involvement in Diabetic Neuropathy With Emphasis on Diarrhea as a Manifestation Thereof Leonard H Brandon Jr[6] (Thayer V A Hosp Nashville Tenn) reports a case of diabetic neuropathy with diarrhea and so little peripheral neuritis initially that the correct diagnosis was not suspected

Man 47 with diarrhea and frequent nocturnal fecal incontinence for five months had had diabetes for six years had been hospitalized several times with acidosis but had never been in coma During an exacerbation of diarrhea which did not respond to paregoric sharp pain numbness and sensations of cold in the lower extremities developed Examination revealed intact superficial reflexes Bilateral stocking and glove hypesthesia to pain and light touch extended proximally to the knees and wrists There was slight impairment of vibratory sensation in the ankles but position sense was normal Sweating was irregularly diminished in the extremities X ray studies of the colon upper gastrointestinal tract and small bowel and sigmoidoscopy showed no abnormalities

Rundles reported 27 cases of diabetic neuropathy with diarrhea In 11 patients diarrhea alternated with constipation 6 had recurrent and 10 continuous diarrhea Diarrhea was often nocturnal with fecal incontinence Meals were often followed by gaseous distention

The intermittent character of diabetic nocturnal diarrhea was stressed by Sheridan and Bailey who found nocturnal fecal incontinence in 31 of 50 cases Peripheral neuritis was observed in 22 of 40 patients and elevation of cerebrospinal fluid protein levels in 17 of 18

There is a dearth of material in the English literature on the pathology of the autonomic nervous system in diabetic neuropathy and autonomic nervous system involvement in diabetic neuropathy is frequently overlooked Treatment consists of strict control of diabetes In addition improvement has been ascribed to pregnant mammalian liver extract and BAL

[In spite of Rundles writings many physicians are unaware of the marked gastric retention and the severe diarrhea that may complicate chronic diabetes —Ed]

Pathology of Regional (Segmental) Colitis Harold W

(6) Am J Med 17 866-870 Dec mbe 1954

Neuman and Malcolm B Dockerty (Mayo Clinic and Found) describe the gross and microscopic features in 25 resected specimens This inflammatory disease of unknown origin involves one or more segments of the large intestine but does not begin in the rectum It involved the terminal ileum in 7 of the 25 cases

Grossly the colonic lesion showed longitudinal shortening of the involved segment circumferential constriction excessive amounts of mesenteric fat surrounding the diseased portion conspicuous thickening of the wall narrowing of the lumen and ulceration of the mucous membrane The ulcerative process grossly apparent in 17 specimens was usually diffuse throughout the involved segment but occasionally was segmental Between ulcerations the mucosa may be smooth and thin hypertrophic or may contain polypoid hyperplasia The change from involved to normal appearing intestine was sharp and rapid

Microscopic changes included ulceration of the mucosa and submucosa but not usually of the muscularis propria The ulcer bases were surrounded by broad or narrow zones of acute and subacute inflammatory cells extending deeply into the wall In the submucosa the granulomatous aspects of the lesion were most apparent with noncaseating giant cell systems seen in 11 of 25 specimens

The regional mesenteric lymph nodes were obviously enlarged in only two cases Twenty nodes showed microscopic evidence of chronic inflammation giant cell systems were seen in four specimens

In seven specimens showing ileal extension thickening of the ileal wall was prominent Microscopically the mucosal lesion was almost identical with that observed in the colon Ulceration inflammatory infiltration and proliferation of fibrous tissue were consistently found Giant cell systems were noted in two instances in the submucosa and twice also in the muscular layers

The lymph nodes from the mesentery of the terminal ileum were enlarged in three specimens normal in four and contained granulomas in two

Microscopically neither the colonic nor the ileal lesion extended more than 6 cm beyond its gross limits Pathologic changes at 3 cm from the lesion included areas of mu

(7) S rg Gynec & Ob t. 99 572 579 N ember 1954

cosa where the glands had been destroyed and replaced by connective tissue infiltrated by lymphocytes and plasma cells fibrous scarring of the submuco a and foci of lympho cytes and plasma cells in the muscularis propria Failure to excise widely enough beyond the gross limits of the le sions is probably not a significant factor in recurrence

The earliest pathologic lesion in the intestine may be purulent cryptitis followed by microscopic abscess forma tion and ulceration of the overlying mucosa These observa tions differ from those of Warren and Sommers who stated that in nonspecific ulcerative colitis as a whole the in flammatory process is exudative and reparative without any granulomatous tendencies

Clinical Study of 201 Cases of Regional (Segmental) Colitis Harold W Neuman J Arnold Bargen and Edward S Judd Jr[8] (Mayo Clinic) reviewed the records of 106

RESULTS OF TREATMENT IN 99 MEDICAL AND 35 SURGICAL PATIENTS

R cur ences	No P t n	%	A F t w u r
Medical			
None	33	33.3	6 75
Single	34	34.3	4 10
Multiple	28	28 3	7 90
Total	95		
Surgical			
None	16	45 7	4 90
Single	9	25 7	3 35
Multiple	4	11 4	6 35
Total†	29		

F pat t h d pon t t eatment.
†Th ee patient d ed in mmed t post pe t period th d ed w th ix month f operation

female and 95 male patients of whom 47 (23 4%) were Jewish

Diarrhea was the chief symptom in 149 about half hav ing three to five bowel movements in 24 hours Eleven had blood in the stools without diarrhea Frank intestinal hem orrhage had occurred in six others

In 131 patients the lesion involved segments of the right and left halves of the colon in continuity and in 15 patients the halves were affected separately In 30 the disease was

(8) S rg Gynec & Obst 99 563 571 November 1954

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[8] S g Gynec & Ob t 99 563 571 November 1954

confined to the right half and in 25 to the left half of the colon The most frequent intestinal complication was inflammatory polypoid hyperplasia of the colonic mucosa *followed by such perirectal and perianal suppurations as* abscesses fistulas and sinuses

Before the first visit to the clinic 47 patients (23 4%) had had surgery Recurrences after medical and surgical treatment are compared in the table There was a high incidence of recurrence after medical treatment but also a greater incidence after surgery than has been reported previously

The number of patients who had recurrence after short circuiting operations was not significantly greater than after resection for the same length of follow up Furthermore the first recurrence after resection was more likely to result in extension of the lesion to the rectosigmoid and rectum than after short circuiting operations

Cortisone in Ulcerative Colitis Preliminary Report on Therapeutic Trial S C Truelove and L J Witts[9] (Radcliffe Infirm Oxford) studied the effect of cortisone orally in ulcerative colitis by treating 109 patients with cortisone

EFFECT OF TREATMENT ON WHOLE SERIES

CLINICAL STATE AT END OF TREATMENT	CORTISONE GROUP	CONTROL GROUP
Remission	45 (41 3%)	16 (15 8%)
Improved	30 (27 5%)	25 (24 8%)
No change or worse	34 (31 2%)	60 (59 4%)
Total	109 (100%)	101 (100%)

Chi squared=21 2 &= P<0 001

and 101 with placebos The double blind technic was observed but the physician was free to stop treatment if he considered it harmful Routine medical treatment could be used in addition to specific therapy at the physician s discretion

Cortisone was given for six weeks 100 mg /day to 38 patients An equal number received the same amount for two to three weeks only followed by 50 75 mg /day Seventeen received more than 100 mg cortisone daily and in 16 the therapy was discontinued before completion

Results shown in the table demonstrate that patients re

(9) B t. M J 375 378 Aug 14 1954

ceiving cortisone enjoyed a clearcut advantage over those on placebos Thus about two of every five on cortisone were in clinical remission at the end of six weeks treatment *compared with less than one of every six getting placebos* A small number treated with cortisone relapsed shortly after the treatment Of 27 patients in remission at the end of treatment with cortisone 2 relapsed shortly afterward of 18 who were improved 2 had an exacerbation when treatment ended

Perforation of the bowel occurred in only two of the control group Massive intestinal hemorrhage developed in one receiving large doses of cortisone Twenty three patients 9 of the cortisone group and 14 of the controls underwent ileostomy during or shortly after treatment because of failure of medical measures Fifteen deaths occurred during or soon after treatment 5 among the cortisone group and 10 among the controls Seven of the deaths occurred among patients who underwent ileostomy

Although not statistically significant in all categories differences in the over all clinical picture in sigmoidoscopic appearances in barium enema findings in the necessity for surgery and in the incidence of early deaths all indicate that cortisone is beneficial in acute ulcerative colitis

Ulcerative Colitis Therapeutic Effects of Corticotropin (ACTH) and Cortisone in 120 Patients were studied by Joseph B Kirsner and Walter L Palmer[1] (Univ of Chicago) *The disease was mild in 6 patients moderate in 52* and severe in 62

Treatment included bland diet sedatives antispasmodics and sulfonamides alone or with antibiotics Initial dose of ACTH was 30 units intramuscularly every six hours and of cortisone orally 200 or 300 mg /day Reduction of dose was *determined by individual response and was made* gradually occasionally ACTH was increased temporarily to 160 units daily ACTH was the dominant therapy in 108 patients 39 also received cortisone at different times usually to maintain the improvement induced by ACTH and occasionally for relief of mild symptoms Cortisone alone was *administered to 12 patients*

ACTH intravenously 20 units in 500 ml of 5% dextrose

(1) A I t. M d. 41 23 250 A gu t 1954

in distilled water once or twice in 24 hours induced maximal adrenocortical stimulation The clinical improvement in 14 patients not responding adequately to ACTH intramuscularly was striking

In at least six patients the clinical response and eosinopenic effect decreased steadily during prolonged intramuscular injection of ACTH However, intravenous administration temporarily controlled symptoms effectively in all instances Increasing unresponsiveness to prolonged or repeated intramuscular injection of ACTH has been observed by others

In the 108 ACTH treated patients the response was good in 70 and moderate in 24 68 had recurrences but many were less severe than previous attacks There were seven deaths three possibly attributable to corticotropin

Response to cortisone was good or moderately favorable in 9 of 12 patients but clinical effects were less striking than with ACTH The advantages of cortisone were fewer side effects and easier administration by mouth

Pre existing anxiety or depression increased in 13 patients and culminated in psychotic episodes in several The ACTH precipitated psychosis was especially severe in one Alkalosis and hypokalemia were associated with emotional disturbances only occasionally Two patients committed suicide

Giant ulceration of the colon was not ob erved possibly because x ray examinations were not repeated during treatment However x ray appearance of severe ulcerative colitis usually does not improve until after long remission of symptoms

Hypokalemia was noted in 23 patients and was pronounced in 2 following diuresis by mercurials Because of increased diarrhea potassium salts were not prescribed routinely Glycosuria was present in 25 of 99 Leukocyte counts rose temporarily in 62 of 92 patients Edema occurred in 102 rounding of the face in 81 acne in 69 and hypertension in 35 Other side effects were flatulence in 38 withdrawal syndrome in 16 headaches in 6 and vertigo in 2

Follow up was less than a year in 45 patients and exceeded three years in 10 Medical management controlled symptoms effectively in 77% 10% did not improve significantly

but continued therapy 7% required surgery and mortality approximated 6%

[A fair evaluation of the place of cortisone and ACTH in the treatment of ulcerative colitis is provided by the two preceding articles Obviously the predictions of neither the extreme optimists nor the pessimists are being fulfilled The efficacy and safety of long term therapy require further study as does the impression gained in some cases that the second course of ACTH or cortisone is less effective than the first —Ed]

Management of Anorectal Complications of Chronic Ulcerative Colitis Raymond J Jackman[2] (Mayo Clinic) found anorectal complications in 32 (16%) of 200 consecutive cases of chronic ulcerative colitis The most frequent complications were pseudopolyps or polyps occurring in 22 patients (11%) Initially at least a polyp is a pseudopolyp or an inflamed mucosal tag There may be considerable variation in the size of an individual polyp depending on the state of the colitis Polyps were fulgurated in 13 patients with no serious untoward effect In nine fulguration was contraindicated because of activity of the colitis or because a stricture prevented adequate exposure of the polyps

Stricture developed in 19 patients (9 5%) It most commonly occurred in the last few centimeters of the rectum resulting from repeated occurrences of internal abscesses and consequent fibrosis of the submucosa and muscularis and narrowing of the rectal lumen Early treatment of abscesses will do much to prevent strictures Stricture also may result from healing of a portion of the rectum that has been denuded of mucosa In several cases the stools could be passed through a small lumen and the patients did not know that they had rectal stricture Operation was performed on only two patients In both the stricture was of the diaphragmatic type and there was little evidence of activity of colitis at the time of operation

Anorectal abscess and fistula were seen in 15 patients These should be considered major complications of chronic ulcerative colitis and the manner in which they are treated may alter the course of the colitis Antibiotics have been ineffective Incision and drainage should be performed under general anesthesia preferably by thiopental sodium intravenously Although this operation may result in an indolent wound anorectal abscesses may recur and cause

(2) A M A A b I t M d 94 420 424 S pt mb 1954

rectal stricture rectovaginal fistulas and anal incontinence if the operation is not performed In all cases the results of surgery were gratifying

Anal fissure spontaneous indolent ulcer or ulcer resulting from a previous anal operation was present in nine patients If the patient s general condition will permit excision of an overhanging edge of skin this procedure frequently will be followed by healing of a fissure or an ulcer It was effective in three patients

Incompetence of the anal muscles usually results from recurrent abscesses causing fibrosis with immobilization of the muscles Anal incontinence also may result from fistulectomy followed by long continued packing of the wound Many instances of incontinence could be prevented by performing a fistulectomy when the patient s condition permits An attempt to relieve incontinence was made in only one of three patients

Ulcerative Colitis Follow up Studies Frank C Wheelock Jr and Richard Warren[3] (Harvard Med School) report data on 343 of 483 patients with ulcerative colitis who could be followed for 10 years or until death Of this group 155 (45 3%) were living and 188 (54 7%) were dead Ul

TABLE 1—RESULTS OF NONOPERATIVE TREATMENT

RESULT	PATIENTS TRACED	TOTAL PA I NTS
Death without operation	74(19 1%)	74(15 3%)
Eventual operation	232(60 0%)	232(48 0%)
Survival without operation	81(20 9%)	81(16 7%)
Not known	—	96(19 8%)
Totals	387	483

TABLE 2—DURATION OF DISEASE BEFORE DEATH OR OPERATION*

DURA ION	B FORE D ATH WITHOUT OPE TION	BE ORE OPERATIO
Less than 3 mo	11(23 9%)	35(17 9%)
3 12 mo	6(13 1%)	29(14 7%)
1 3 yr	10(21 8%)	50(25 6%)
3 5 yr	5(10 7%)	20(10 2%)
More than 5 yr	14(30 5%)	62(31 6%)
	46	196

* D rat on c uld n t be e tabl hed n 36 of the earl e cas s

(3) New Engla d J Med 252 4 1-425 Ma 17 1955

cerative colitis was responsible for 153 (81 2%) of the deaths peritonitis hemorrhage toxicity and carcinoma of the colon being the immediate cause

With the addition to the study group of 44 patients who required surgery but could not be followed it was found that 20 9% of the group survived without operation (Table 1) As it is probable that many of the untraced patients also did well the percentage of those who avoided operation might actually be almost 50% Duration of the disease be fore operation was necessary or death occurred is shown in Table 2

Of 319 patients who lived 10 or more years after onset of ulcerative colitis and who did not have colectomy before 10 years 28 (8 8%) had colon carcinoma The true figure is probably higher if one considers also the possible incidence of colon carcinoma among the patients who were lost to follow up

Surgery was performed in 47% of cases between 1915 and 1942 and in 44% during 1943-47 After surgery 18 had 26 episodes of small bowel obstruction This occurred in patients with colectomies as well as in those who had ileos tomy only No true ulcerative colitis was seen developing proximal to an ileostomy Indication for surgery are as fol lows if after two to three years of nonoperative manage ment the colonic changes as seen by proctoscopy and x ray studies are considered irreversible colectomy and ileostomy offer the safest course even if the patient is asymptomatic

[Two reservations are made by the authors themselves (1) the course of ulcerative colitis between 1915 and 1949 is not necessarily the course of ulcerative colitis today and (2) 140 of 483 patients were lost to follow up Nevertheless the figures give a grim indication of the severity of the illness in hospitali ed patients and provide a background against which the efficacy of ACTH adrenal steroids or any other treat ment can be judged —Ed]

Chronic Ulcerative Colitis Early and Late Experiences of 124 Patients with Ileac Stomas Arnold G Rogers J Arnold Bargen and B Marden Black[4] (Mayo Clinic and Found) reviewed 70 males and 54 females seriously ill with chronic ulcerative colitis who were treated by ileostomy in 1940 through 1949 Follow up to 1952 included 93% of the

(4) Gastroenterology 27 383 399 Oc obe 1954

patients The total was close to 5% of all patients with chronic ulcerative colitis seen in the same period

The most important indications for ileostomy were complications primarily occurring as sequelae of disease in the colon itself Polypoid or adenomatous changes in the colon occurred in 65% stricture of some part of the colon in 52% and severe perianal infection in 43% Abscesses fistulas incontinence and history of unsuccessful anal surgical treatment were common Rectovaginal fistula was present in 22% of the women and rectovulvar fistula was often present Carcinoma occurred in 15% of the patients Some had benign strictures *Other indications included perforation of the* colon obstruction abdominal mass failure of other surgical treatment and enterocutaneous fistula Intractability with chronicity was an indication in 4%

By 1952 57 of the group (46%) had died having lived less than one year on the average Hospital mortality rate was 23 4% (29 deaths) Death was due to peritonitis in 16 patients Symptoms of colitis continued in 41% of the patients after ileostomy Many patients led normal lives pursuing their usual vocation

Eight patients (6%) had severe hemorrhage from the stoma mainly due to enteritis which was found in 15 (12%) on further examination Serious intestinal obstruc*tion developed in 57 and minor episodes in many more* Multiple causes included adhesive bands retraction and stenosis of the stoma stomal prolapse metastatic carcinoma postoperative dysfunction and intraluminal obstruction from high residue foods Nine patients were never free from discomfort due either to the thought of the stoma or to local distress caused by it Patients surviving one year after the ileostomy and having no serious complications represented only 14% of the entire group

A second operation for prolapse stenosis or fistula formation was necessary in 38% of ordinary and 33% of skin grafted stomas Surgical revision of the stoma for other reasons brought the total number of patients needing revision to 53 (43%) The number of revisions for these patients averaged between one and two per person It should be emphasized to the patient that the stoma is permanent otherwise there is great demand for closure

The study indicates that in many cases the stoma may prove to be a far greater disability than is generally real ized

[Although immediate colectomy is proving a more satisfactory opera tion for ulcerative colitis than simple ileostomy (witness the 41% who had continuing colitis after establishment of the stoma) the psychiatric, physiologic and hygienic problems created by the ileal stoma remain very much with us The high incidence of ileac stoma dysfunction obstruction and disease makes it imperative that the characteristics of the normal stoma be better known The following article is valuable for this pur pose It is surprising however that the pre stomal ileum which gradual ly assumes the functions of storing and desiccating chyme should present a normal caliber —Ed]

Roentgen Observations of Ileostomy in Patients with Idiopathic Ulcerative Colitis I The Well Functioning Ileostomy Felix G Fleischner Paul Mandelstam and Ben jamin M Banks[5] (Boston) point out that postoperative ileal dysfunction is a relatively common complication of ileostomy

In 13 patients with a well functioning ileostomy for six months or longer the small intestine was studied both by barium enema through the ileostomy stoma and by oral passage of barium water suspension Ileostomy done for severe idiopathic ulcerative colitis had been combined with partial or total colectomy in 11 instances

Criteria for selection were restoration of normal body weight freedom from colicky abdominal pain and other evidence of partial obstruction and normal volume con sistency and odor of ileal discharge Mild to moderate pro lapse was disregarded Eleven patients were leading nor mal fully active lives Two others with involvement of the terminal ileum besides severe colitis at the time of opera tion had x ray evidence of localized disease of the prestomal ileum However because of good general health and absence of ileostomy dysfunction they were included in this series

The time since ileostomy varied from 13 months to 11 years The time from the last episode of ileostomy dys function warranting medical attention varied from ½ to 7 years

In 6 of the 11 patients without x ray evidence of ileal disease the width of the prestomal ileum was within nor mal limits This is contrary to the prevailing view The

(5) R d l gy 63 74 80 J ly 1954

barium enema study revealed Kerkring's folds extending down to the stoma (Fig 91) in all but the two patients with ulceration of the prestomal ileum in whom the folds *were absent for 25 30 cm Study of the oral passage of*



Fg 91—Spot film taken during flow f bari m th ugh ileo tomy F l y c th ter in pat nt wh h d u dergone ght lect my a d leo tomy I flated balloon s een n front f 5th l mba vert b a P e t mal ileum is norm l in width and c e lar mucosal f ld e bl down to balloon (Courte y of Fle schner F G t l Rad ol gy 63 74-80 J ly 1954)

barium did not reveal any abnormality Transit time was normal

Presence of formed fecal matter in the prestomal ileal segments *in three patients in two of whom the colon had* been completely removed supports Ogilvie's contention that the lower ileum is capable of inspissating its content whether or not the colon has been removed

Colonic Bleeding and Diverticular Disease   lon Carl

S Hoar and William F Bernhard[6] (Peter Bent Brigham Hosp) reviewed the records of 385 patients with diverticulosis and diverticulitis Thirty eight had carcinoma of the colon and rectum but in only 14 was it in the area of diverticula

Of 111 patients with diverticulitis but not carcinoma 31 had only occult bleeding and were not anemic 9 had gross blood or strongly guaiac positive stools and 2 had massive rectal bleeding which required immediate surgery Of 236 patients with diverticulosis but not carcinoma 39 had rectal bleeding Of the 39 18 passed bright red blood before hospitalization and 21 with diverticulosis proved by barium enema had guaiac positive stools and no clinical or roentgen evidence of any other bleeding site

The authors report in detail four cases of massive bleeding associated with diverticulitis in three men and one woman aged 62 72 In Case 1 four of five sectioned diverticula found on the resected specimen of sigmoid colon showed granulation tissue replacing part of the mucosa the lining of one was superficially ulcerated with hemorrhage into the granulation tissue At autopsy no other source of rectal bleeding was found in the gastrointestinal tract In Case 2 barium enema showed an area of spasm in the sigmoid colon and numerous scattered diverticula No bleeding occurred after operation but the patient died on the third post operative day autopsy was refused In Case 3 the surgical specimen showed extensive diverticulitis with edema and induration several diverticula were ulcerated Autopsy showed no other ource of bleeding In Case 4 the resected specimen showed chronic diverticulitis but no definite bleeding point Five months after operation there had been no recurrence of bleeding

In massive rectal bleeding early operation for diverticular disease is essential especially in elderly hypertensive patients if the upper gastrointestinal tract is clear ulcerative colitis is absent on proctoscopy and diverticula are found on x ray

[This study is repre entative of many appearing in the current literature if in a series of patients occult or frank blood is found in the stools and rad ologic studies reveal nothing beyond intestinal diverticula the conclusion is reached that the two conditions must be causally re

(6) S rg Gynec & Obs 99 101 107 J ly 1954

lated This is treacherous business It should be recognized that occult blood appears in the stools especially transiently for reasons that are often difficult to ascertain Feces giving positive reactions to tests for occult blood but not containing fresh blood are furthermore practically never the result of lesions in the distal colon Finally diverticulosis of the colon is such an extremely common condition that it will be found in many patients with gastrointestinal blood loss merely on the basis of mathematical chance As opposed to chronic or occult blood loss however diverticulitis is a cause of brisk to massive bleeding from the lower bowel The serious nature of this type of case is deservedly emphasized —Ed]

Occasional Discrete Polyps of Colon and Rectum Showing Inherited Tendency in a Kindred Charles M Woolf Ralph C Richards and Eldon J Gardner[7] (Univ of Utah) investigated the incidence of occasional discrete (solitary) polyps of the colon and rectum in a large Utah kindred Six members of one generation of this kindred died from cancer of the gastrointestinal tract which was located four times in the lower part of the tract

Sigmoidoscopy was performed on 55 members of the third generation aged 26-69 (average 51 7) and on 21 spouses of this generation serving as controls Among the former 25 had one or more polyps and among the latter there was only one questionable polyp Thirty four polyps were removed Pathologically none was carcinoma

The 45% incidence of polyps among the members of the third generation of this kindred is much greater than the frequency of about 5% found in the general population Since any environmental agent present in the homes or communities of the kindred members and leading to the occurrence of polyps would also manifest itself in the spouses it is postulated that a hereditary factor is playing an important etiologic role in the occurrence of occasional discrete polyps in this kindred This hypothesis would account for the high incidence of polyps in the generation investigated as well as for the four cases of carcinoma of the lower digestive tract that occurred in the previous generation

Amebiasis Controlled Linear Studies on Nondysenteric and Mild Hepatic Forms in Egyptians H Leonard Jones Jr Gamil Cassis Thomas M Floyd and N S Mansour[8] (USN) studied relatively healthy Egyptian employees to

(7) Cancer 8 403-408 Mar Apr 1955
(8) A n Int Med. 42 763 785 Apr I 1955

determine the significance of nondysenteric amebiasis Microscopic examination of fresh stools prepared by the merthiolate® iodine Formalin technic identified three parasitologic groups (1) a *mixed* group with both large and small Endamoeba histolytica trophozoites cysts or both (2) a *small race* group with only small tropho oites cysts or both and (3) a *control* group with persistently negative stools

Twenty one subjects were studied before and 23 after

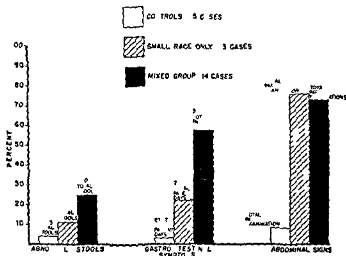


Fig 9 —Comp r of f quen a f b mal stool g t o nt s l d abdominal s gn c mb d p e a d post t atment gr ups f Egyptia mpl yees. (Court y f J t H L J t l An I t M d 4 763 785 Apr l, 1955)

treatment consisting of (1) a placebo for 2 weeks (2) 0 25 Gm vioform® four times daily for 15 days and (3) 0 25 Gm carbarsone® *twice daily for 10 days*

In seven subjects with either or both races before treatment and persistently negative stools after treatment frequency of abnormal stools was five times and that of flatulence three times less after treatment Abdominal cramps were twice as common before as after therapy

Analysis of the combined pre and post treatment groups showed that clinical abnormalities such as loose stools

sigmoidal tenderness and flatulence were most common in the *mixed* group less prevalent in the *small race* group and negligible in the *control* group (Fig 92)

The present study supports the concept of mild pathogenicity of the small race and shows that apparently healthy carriers of either race may have mild symptoms and signs of amebiasis if followed serially over a long enough period

[An article in the 1954 55 YEAR BOOK (p 559) presented good evidence that many carriers of E histolytica suffer from an irritable colon syndrome no different in etiology and manifestations from that seen in patients without parasites This was welcomed as an effective rebuttal of those who feel that discovery of amebic cysts explains almost any symptom Now Jones and his associates unfortunately provide rather heavy ammunition for the other side—unfortunately, because the carrier state will again be blamed for many psychogenic complaints —Ed]

Serologic Considerations Relative to Diagnosis of Amebiasis John Bozicevich[9] (Nat'l Inst of Health) states that since extraintestinal amebic infections tend to produce protean symptoms and stool examinations fail to reveal any evidence of amebic infection in a large percentage of such cases serologic tests furnish one of the best methods of diagnosis False negative results however occur frequently in intestinal amebiasis and an incidence of up to 13% can be expected in hepatic involvement False positive results were found by the author in 8-10% of several hundred serums

Tobie *et al* found a single direct stool smear 27% and a complement fixation test 25% efficient in cases with intestinal involvement However the efficiency of the zinc sulfate flotation method of stool examination was 64%

It appears that Endameba histolytica antigen will not detect infections with protozoans other than E histolytica There are indications that strain differences in E histolytica do exist Thus it seems that a polyvalent antigen will be necessary for diagnosis of amebiasis by serologic methods

Although in some cases complement fixation may be negative two to four weeks after successful therapy, in others it may remain positive up to three years In most instances however the antibody titers drop after therapy

Treatment of Enterobius Vermicularis Infections with Piperazine Animal experiments have shown that pipera

(9) Am. J Gastroente l 23 332 334 Apr l 1955

zine is very effective against adult worms but only slightly against immature pinworms Therefore interrupted treat ment over several weeks was suggested to allow immature forms to develop to the mature susceptible stage However even with such a schedule infection in the family and self infection were still possible Besides a shorter therapeutic regimen if equally effective would be advantageous

H W Brown and K F Chan[1] (Columbia Univ) treated 120 pinworm infested persons aged 1 52 for 10 and 14 con secutive days according to the dosage schedule given in the table

The 10 day course eliminated 89% of the infection the split 14 day treatment (7 days of therapy 7 of rest 7 of therapy) 92% and the 14 day treatment 97% No com plaints side effects or toxicity from piperazine citrate were noted

DOSAGE SCHEDULE

W igh L	P p r ne C trate S up	Equ v P1 az n H hy at
15 30	/ tsp (2 5 cc) b i d	0 25 Gm b i d
31 60	1 tsp (5 cc) b i d	0 5 Gm b i d
61+	2 tsp (10 cc) b i d	1 0 Gm b i d

The authors feel that as enterobiasis is a mild and often asymptomatic infection use of toxic or relatively nontoxic drugs in amounts large enough to produce side effects is un warranted

Treatment of Cases of Ascariasis with Piperazine Citrate With Observations of Effect of Drug on Other Helminthi ases Clyde Swartzwelder Joseph H Miller and Robert W Sappenfield[2] (Louisiana State Univ) gave piperazine cit rate to 26 patients with uncomplicated intestinal ascariasis with light and heavy worm burdens for 3 15 days Twenty two of 25 patients had 100% reduction of the egg counts No treatment failures occurred in patients receiving about 75 mg /lb daily for five days and this dosage may even eliminate some infections in one to two days Both mature and immature ascarids were eliminated from the intestine They were still alive when passed during therapy but most of those observed were sluggish or flaccid Daily dosage of

(1) Am J T op M d 4 3 1 3 5 M h 1955
( ) Ib d pp 3 6 331

70 75 mg /lb for four or more days apparently is more than is required to cure most light infections In heavy infections such a dosage was usually completely effective and well tolerated by the children Close observation failed to reveal any side reactions

[Toxic reactions to piperazine (marketed under the name of antepar®) do occur if large doses are used but the drug appears relatively safe and should prove a welcome addition to gentian violet and hexyl resorcinol —Ed]

Significance of Intestinal Decomposition Products of Cellulose on Effect of Cellulose Laxatives is discussed by Pekka Brummer[3] (Turku Finland) The laxative effect of various hygroscopic celluloses used widely in treating constipation is usually ascribed to their property of increasing the bulk of stools In addition the chemical products arising from decomposition of celluloses by intestinal micro organisms may stimulate the bowel the lower volatile fatty acids have the greatest stimulating power

To learn which of these stimuli causes the laxative effect of celluloses comparative experiments were carried out with methyl cellulose powdered nonhygroscopic berry husk cellulose and lactose which is not readily absorbed

Feces were studied in vitro by the Schmidt Strasburger fermentation test either using the sample alone or adding 1 Gm powdered methyl cellulose berry husk cellulose or lactose The fecal aqueous suspension was kept for 24 hours at *37 C* and the amount of gas produced determined and used as the measure of carbohydrate fermentation In 10 tests both methyl and berry husk cellulose nearly doubled the volume of gas produced Lactose increased gas formation by four demonstrating that it is most readily decomposed by fecal micro organisms

For 1½ 3 weeks 10 15 Gm berry husk cellulose was given daily to 14 and the same amount of lactose to 12 constipated patients Each substance was also given to normal persons Thirteen patients received 6-10 Gm methyl cellulose a day Berry husk cellulose and lactose had no effect on the number and consistency of the stools but methyl cellulose had a definite laxative action in three and milder action in two No preparation affected results of the fermentation test or pH of stools

The laxative effect of methyl cellulose is probably based

(3) Ga t oent logia 8 10 14 J ly 1954

on its ability to increase the bulk of the stools and not on irritating chemical products of intestinal decomposition This is borne out by the observation that lactose in the doses used had no laxative effect although it was given in enteric coated tablets to retard absorption

Clinical Comparison of Bulk and Stimulant Laxatives Leo J Cass and Willem S Frederik[4] (Boston) suggest randomized sequence of administration and double blind conditions in evaluating laxatives The preparation of medication method of coding and choice of placebo or control should be carried out so that neither observer nor subject can identify the medication Thus subjective observations can be placed on a quantitative impartial basis for comparing medications

Substances given 45 semiambulatory institutionalized

COMPARISON OF LAXATIVE MEDICATIONS

T A M N	No PA N	Bow M M 10	
		Av	S D
Lactose	44	5 614	3 507
Methylcellulose	45	8 044	2 565
Milk of magnesia	44	9 072	2 518

Sta da d deviat on

severely constipated patients were (1) methylcellulose tablets 0 5 Gm (2) milk of magnesia tablets (magnesium hydroxide powder at 73%) 0 444 Gm and (3) laxative tablet (placebo) milk sugar 0 4 Gm Four tablets were given in the morning and four at night

As shown in the table milk of magnesia gave a slightly higher bowel movement frequency than methylcellulose Milk of magnesia increased frequency most rapidly during the first five days of treatment in the last five days there was a slight decrease in frequency for all three drugs

Milk of magnesia as well as methylcellulose definitely softened the consistency of the stools A significant difference in fecal consistency from milk of magnesia or methyl cellulose cannot be proved Tenesmus cramps and a sense of fullness were common in the placebo series Either methylcellulose or milk of magnesia completely abolished these symptoms

Anorectocolonic Side Effects of Antibiotic Therapy Rob

(4) Journ l Lancet 75 105 108 M rch 1955

ert Turell and Aubre de L Maynard[5] (New York) studied 136 patients with an anorectocolonic syndrome that followed in 125 oral administration of a broad spectrum antibiotic and in 11 erythromycin Diarrhea as the sole complication usually appeared 12 72 hours after ingestion of the antibiotic and was noted in 37 patients diarrhea with anal or anogenital pruritus occurred in 22 the itching appearing with or several days after the diarrhea 51 had pruritus alone

The diarrhea varied from one to two loose stools a day to moderate dysentery with blood and pus The latter was observed in three patients three to eight days after 250 mg chlortetracycline or oxytetracycline every six hours all three had previously received penicillin without reaction The endoscopic picture resembled nonspecific ulcerative colitis

Sigmoidoscopy of patients with mild diarrhea after chlortetracycline oxytetracycline or erythromycin showed no or only slight abnormalities X rays of the colon were normal except for variable spasm Anal pruritus without diarrhea appeared several days to weeks after chlortetracycline oxytetracycline erythromycin or tetracycline

The three patients with dysentery showed micrococci on smear which responded promptly after discontinuation of the causative antibiotic to administration of large doses of carbomycin or erythromycin Identifying the causative organism and using proper antibiotic are important but it should be remembered that some organisms have already developed a resistance to erythromycin Most of the other cases of diarrhea responded to paregoric castor oil a diet high in protein carbohydrate and vitamins and discontinuation of the offending antibiotics Anal pruritus disappearing in some patients spontaneously was well controlled in others by discontinuing the offending antibiotic prohibiting use of dry toilet paper and topical application twice daily of an ointment containing 5% sodium caprylate and 5% sodium propionate with oral phenobarbital or bromides In some instances steroids were helpful Acidophilus milk (yogurt) was of no benefit Sodium caprylate orally which recent studies show had good results in intestinal moniliasis helped several patients but failed in others

(5) J A.M.A. 156 217 2 0 S pt 18 1954

The study supports the view that while micrococcic enteritis is serious the anorectal syndrome though annoying is not

[Some preparations designed for anal application contain one or more antibiotics Such preparations might prove of dubious benefit for the type of anal disorders here described and it seems imperative that a physician before prescribing an anal ointment or cream know its exact composition of which usually no hint is given by the mellifluous trad name bestowed upon the preparation —Ed]

LIVER GALLBLADDER AND PANCRFAS

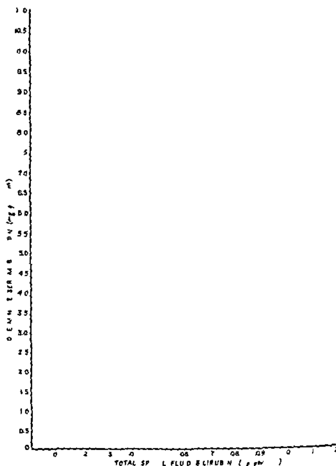
Jaundice and Xanthochromia of Spinal Fluid L B Berman I W Lapham and E Pastore[6] (Boston City Hosp) studied the conditions under which bilirubin may appear in the cerebrospinal fluid of patients with jaundice Simultaneously drawn samples of blood and cerebrospinal fluid from 20 patients with nonhemolytic intra or extrahepatic obstructive jaundice due to various causes and with no evidence of meningeal disease were analyzed for bilirubin An effort was made to determine the relation between serum and cerebrospinal fluid bilirubin in these cases

Eleven cerebrospinal fluids from normal subjects had a total bilirubin content of 0 000 0 011 mg /100 ml Quantitative analysis of specimens from the jaundiced patients revealed 0 01-0 12 mg bilirubin Cerebrospinal fluid containing 0 05 mg or more was consistently xanthochromic

A scattergram made by plotting all total cerebrospinal fluid values against the corresponding one minute serum bilirubin values is shown in Figure 93 In any one patient serial determinations usually revealed parallel fluctuations in the levels of serum and cerebrospinal fluid bilirubin The long standing observation that the brain is not stained even with prolonged jaundice may be related to the relatively low concentrations of bilirubin in cerebrospinal fluids which in present cases ranged from 1 10 to 1 100 of the serum values

Since bilirubin may cross the meningeal barrier in detectable amounts in a matter of days it is believed that in jaundice xanthochromia cannot be used without qualification

(6) J Lab & Cl M d 44 273 279 A gu t 1954



Fg 93—S atte g m f alJ er m b I rubı det rm at on pl tted ga n t c r spond c eb o p nal flu d dete m n t ons (Cou te v of B rman L B et al J Lab & Clın M d 44 73 2 9 A gu t 1954)

as evidence of the presence of subdural hematoma or other causes of ıntracranıal bleeding

Effect of Hepatıtis during Pregnancy on Newborn ıs dıscussed by H Ellegast, G Gumpesberger and F Wewalka[7] (Unıv of Vıenna) One could assume that the hepatıtıs vırus lıke other vıruses mıght permeate the placental barrier

(7) W en kl n Wchnsch 66 507 511 J ly 23 1954

and infect the fetus The authors studied 57 patients who had hepatitis (mostly serum hepatitis) during pregnancy

Among the babies two were stillborn and four were not viable These six were not jaundiced Only one of the living infants had jaundice presumably viral hepatitis of transplacental origin The rest did not show signs of liver damage up to 2 years of age Of 25 children whose mothers had serum hepatitis during the first few months after delivery 7 died of various causes during the first eight months 1 of acute yellow atrophy of the liver No congenital abnormalities were found among the children of mothers who had hepatitis during or after pregnancy

It is concluded that although viral hepatitis seems rare among fetuses and infants there is a possibility of transplacental infection In most cases maternal antibodies may prevent the disease in the newborn

Effect of Physical Activity on Recovery from Hepatitis Follow up Study Two to Three Years after Onset of Disease Robert S Nelson Helmuth Sprinz James W Colbert Jr Frank P Cantrell W Paul Havens Jr and Marjorie Knowlton[8] (Philadelphia) state that it is impossible to incriminate inadequate rest poor diet or alcohol in development of sequelae following viral hepatitis This was borne out by observations on 79 men serving with the U S Armed Forces in Germany two to three years after recovery from hepatitis During their acute illness the men were kept in bed for at least three weeks or until they were asymptomatic with the one minute direct serum bilirubin less than 1 mg /100 ml Clinical course and severity of the illness were representative of viral hepatitis as seen in service personnel in Germany maximal total serum bilirubin exceeded 5 mg /100 ml in 62% of patients Duration of hospitalization ranged from 25 to 150 days (average 68)

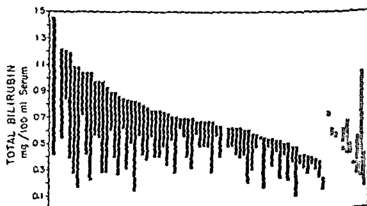
At discharge all but two men were asymptomatic The liver was palpable in nine and tender in three Ten had elevated total serum bilirubin levels 25 had abnormal thymol turbidity tests and a few had abnormal cephalin cholesterol and bromsulfalein tests Abnormalities in hepatic function were however mild in all instan es

On re examination 22 33 months later all men had been

(8) Am J Med 16 780 789 J 1954

able to do full duty Two had had conjunctival icterus briefly on one occasion None had had any known exposure to hepatotoxins but all but five admitted drinking alcoholic beverages daily No consistent weight change was noted

In response to specific questions 22 men complained of one or more of the following symptoms anorexia early fatigability and most often distress in the right upper quadrant In 20 patients the liver was palpable tender or both in 4 spider angiomas were found and 1 had spleno



F g 94.—Amounts f total se um b lirub n found at two xaminat ons in 79 pa t ent Top f ach bl ck bar ep sent m unt at discha ge fr m in t l hosp t l t on bottom of ch bl ck ba amount at e-exam nation 22 3 months lat Bl ck dots rep esent patients whose am nts f serum bil rubin w r th ame at both examin t ons C ss hatched ba s patients whose s rum bil ubin n eased betw en exami ations bottom l n of each r h tched bar amo nt at d scha g fr m n t al hosp tal at on a d t p f ea h b amo nt at re-exami ation (Court sy of N lson R S t al Am J Med 16 780 789 June 1954)

megaly Twenty four had one abnormal liver function test and two others had two The commonest abnormal tests were the thymol turbidity and bromsulfalein test (13 patients each)

Biopsy was performed on 40 patients Only six had abnormal findings such as moderate thickening of central veins increased connective tissue focal necrosis and fatty vacuolation There was no apparent correlation between occurrence of symptoms signs or hepatic functional disturbance and the histologic appearance of the liver

Between discharge and re examination the incidence of

abdominal distress anorexia and easy fatigue increased as did the number of palpable and tender livers In contra t results of hepatic function tests except the bromsulfalein test improved Nine ot 10 patients with increa ed total se rum bilirubin at discharge had normal amounts at re ex amination Even when both types of serum bilirubin were normal at discharge concentrations decreased further sub sequently (I ig 94)

No relation was noted between incidence of abnormali ties at re examination and either severity of the original disease or degree of alcohol con umption during the inter im In no case was there sufficient evidence to justify the diagnosis of chronic hepatitis

The data suggest (1) that hepatic function and histology cannot be predicted on the basis of mild clinical abnormali ties or vice ver a and (2) that physical activity in excess of that usually prescribed in acute hepatiti, does not in hibit sustained recovery in the type of patient studied

Chronic Idiopathic Jaundice with Unidentified Pigment in Iiver Cells New Clinicopathologic Entity with Re port of 12 Cases I N Dubin and Frank B Johnson[9] (Washington D C) state that con titutional hyperbil rubinemia (Gilbert s disease familial nonhemolytic jaun dice 'constitutional hepatic dysfunction) may incorpo rate several ill defined types of jaundice They report 12 cases of a disease belonging to this syndrome which affects young persons and is characterized by chronic or intermit tent jaundice and a gro sly discolored liver which except for brown pigmentation is hi tologically normal The con dition is compatible with normal existence

The patient, gave no history of drug addiction alcohol ism expo ure to hepatotoxins or transfusions with blood products The only past illnesses of interest were episodes of jaundice in six patients Only one patient was symptom free The others complained of right upper quadrant pain epigastric discomfort cramping abdominal pain or back pain Weakness or fatigability was noted by six pa tient anorexia by six nau ea or vomiting or both by four and nervousness by two Dizziness headache fever belch ing and diarrhea were uncommon All patients had jaundice

(9) M d e 33 155 197 S pt mbe 1954

which usually fluctuated in intensity and lasted 8 months to 33 years Some had only scleral icterus The liver was enlarged 1 3 fingerbreadths in five patients and was tender in four Dark urine was noted by six patients

There was no evidence of anemia, hemolysis or erythrocyte abnormalities The Coombs test done on four patients was negative Twenty four hour fecal urobilinogen excretion determined in three cases was normal or low Of 11



Fig 95 —Centr l b la d tr bution f p gm t AFIP asse on no 5?0 5? hem toxyl n e s n ×50 (Co rt sy of Dub I N d J h F B Medicin 33 155 197 S ptember 1954)

patients 8 showed bromsulfalein retention of 10% or more at least once Cephalin flocculation was 3+ or 4+ at some time in six patients but none had persistently abnormal values Thymol turbidity was over 4 units in 6 of 11 patients Serum protein levels were normal in the 11 patients studied

Cholecystography failed to visualize the gallbladder in 10 of 11 patients though it was tried more than once Peritoneoscopy or exploration performed in eight cases revealed a normal gallbladder and biliary tract and no evidence of extrahepatic biliary obstruction

In all cases a coarsely granular amorphous brown pig

ment was found in the liver cells of the centrolobular zones (Fig 95) sparing the Kupffer cells When most abundant it tended to spread from the center to the periphery of the lobules The pigment was neither bile nor hemosiderin and being inert to usual solvents could not be extracted Except for the pigment the liver was normal histologically The canaliculi did not contain bile plugs thus distinguishing this condition from obstructive bile stasis

Various forms of therapy did not change the jaundice Repeated liver biopsies revealed unchanged liver pigmentation Prognosis was excellent

Although the entity described resembles Gilbert s disease in symptomatology age of onset and clinical course there are differences In the present entity a familial factor was present only once the van den Bergh reaction was direct urine was dark in 50% of cases bromsulfalein secretion was often abnormal the gallbladder was never visualized by cholecystography and the liver was discolored In Gilbert s disease familial incidence is frequent the van den Bergh reaction is indirect urine is light bromsulfalein values are normal the gallbladder is visualized on cholecystography and the appearance of the liver is normal

Liver biopsies in about 1 000 cases of viral hepatitis in all stages did not show the histologic picture characteristic of the pigmented liver and it is unlikely that this condition arises as a phase or sequel of viral hepatitis

This new entity is believed due to an inborn deficiency of the liver characterized by multiple defects in metabolism whereby the liver cannot properly excrete bilirubin the pigment which accumulates in liver cells bromsulfalein and dyes used in cholecystography

[From the viewpoint of hepatic function, the patients here described seem to suffer from a fairly serious liver affliction. The bilirubinuria the bromsulfalein retention the occasional abnormal results of flocculation tests and the abnormal results of cholecystography certainly make this condition vastly different from so-called constitutional hepatic dysfunction and make the reader doubt that these cases represent as the authors suggest, an inborn deficiency of the liver —Ed.]

Obstructive Type Jaundice Due to Chlorpromazine (Thorazine®) Report of Three Cases Ray A Van Ommen and Charles H Brown[1] (Cleveland Clinic) state that in patients treated with chlorpromazine jaundice may develop

(1) J A M A 157 3 1 3 5 J 22 1955

insidiously or suddenly with mild grippe like symptoms with or without fever Changes in bowel habits, abdominal distress nausea and occasional vomiting may occur Subsequently jaundice liver tenderness pruritus clay colored stools and dark urine appear The urine contains bile and little urobilinogen Serum bilirubin alkaline phosphatase and cholesterol levels are elevated Tests for hepatocellular damage uniformly show unaltered results Thus the clinical and laboratory picture simulates obstructive jaundice This should be considered in differential diagnosis to avoid unnecessary surgery

The authors three patients who had jaundice received 75 150 mg thorazine® daily for two to three weeks In one the serum bilirubin rose to 18 8 mg/100 ml direct and 14 7 total

The incidence of jaundice induced by chlorpromazine is low Although in most cases it disappears in two to four weeks cases have been reported in which it lasted two and seven months The first of the authors patients was recovering after 12 weeks while the third was still jaundiced after 3 months In the first patient operative liver biopsy revealed cholestasis in the biliary canaliculi with no evidence of liver cell damage ACTH 40 mg daily did not prevent increasing bilirubinemia

The delay of two to three weeks before onset of jaundice along with the occasionally noted eosinophilia (42% in one case) might indicate hypersensitivity or allergic reaction however slow response to steroid therapy speaks against it

[Although the incidence of thorazine® jaundice is estimated at no more than 1% of those receiving the drug for two weeks thorazine® is used so extensively that the absolute number of cases is considerable The dose and duration of therapy necessary to produce jaundice vary widely from case to case but surprisingly several large series of psychiatric patients receiving huge doses of the drug are said to have escaped without a single instance of jaundice

The principal features of the clinical picture are early malaise and fever eosinophilia (between 25 and 50% of cases) and liver function tests that point to biliary obstruction A new liver function test however has now become necessary keep a tablet of thorazine® in the pocket show it to every jaundice patient and ask him if he has ever taken anything like it —Ed]

Aspects of Nutritional Liver Disease—Human and Experimental Joseph Gillman and Christine Gilbert (Univ

(2) A n New Y k A d S 57 737 749 1954

of Witwatersrand) studied the relationship of hepatic fibrosis to antecedent fatty change and to necrosis of the liver in malnourished human beings and in animals fed various diets They demonstrated by liver biopsies in infant pellagrins that under therapy large accumulations of fat may disappear from the liver within 14 days and that a mildly fatty liver can become intensely fatty within 8 days

The fatty change in the livers of infant and adult Africans is of relatively acute onset and usually disappears after the acute episode Sampling of the livers of the general population at all ages does not show a persistent and progressive fatty change Since evidence of hepatic fibrosis cannot be correlated with frequency of hepatic steatosis it is suggested that the fatty liver per se in the malnourished African with an acute nutritional breakdown does not promote the high incidence of liver disease in Johannesburg On the other hand a fibrotic liver can undergo a fatty change it is possible to mistake the sequence of these two reactions and to regard the fatty change as preceding the *fibro is It is felt that accumulation of fat and overgrowth* of fibrous tissue in the liver are end results of two separate processes not necessarily causally related

Acute liver necrosis has not been established in infant and adult Africans hospitalized during an acute nutritional breakdown In one pellagrin thiamin precipitated diffuse necrosis recognized on liver biopsy

Animal experiments revealed that although survival on a necrogenic diet can be prolonged by occasional feeding of a balanced ration the liver remains vulnerable and can become grossly affected later If the animal receives a balanced diet regeneration of the liver results The mechanism responsible for necrosis is not identical with that favoring fibrosis Both require special metabolic conditions and in man both can be induced in the liver by diet Diet may lead to fibrosis by rendering the liver more vulnerable to noxious agents and by promoting fibrosis once necrosis has supervened

In the causal relationship between contents of the diet and onset of liver necrosis emphasis should be placed not on factors lacking in the diet but on its constituents which create the conditions for making a specific nutrient a lim*iting factor in a nutritional syndrome Explanations of the*

complex chemical processes underlying production of the fatty liver in terms of single factors are untenable as is well shown in the case of milk Though dried skim milk is efficacious in treating malnourished infants it contains besides proteins, other factors which prevent hepatic damage

It is evident that a minimum number of nutrients must be present in the diet to promote accumulation of fat in the liver The nature of the metabolism stimulated by these nutrients provides the setting in which proteins may be alipotropic at one level and lipotropic at another The role of a nutrient in prevention of the fatty change is therefore a function of the metabolism promoted by the other constituents of the diet Unless this is appreciated unexplained paradoxical reactions will occur in nutritional investigations Thus the addition of 10% food yeast to potato starch results in a 95% incidence of hepatic necrosis in young rats whereas a diet of 10% food yeast and 90% maize meal is associated with severe bone deformities

Several investigators have disclosed that in certain circumstances feeding excessive amounts of one amino acid can excite severe toxic reactions in experimental animal such as acute pancreatic necrosis after excess of tyrosine An abnormally high concentration of an amino acid sharpens the need for particular vitamins and other food factors in amounts out of proportion to the requirements of the organism subsisting on a different diet

Clinical Aspects of Treatment of Kwashiorkor common in certain tropical countries are described by H C Trowell[3] (Makerere College Kampala Uganda) Kwashiorkor occurs mainly in young children and follows prolonged consumption of a high carbohydrate low animal protein diet of poor variety Adults occasionally have a similar disorder

In severe kwashiorkor the child 9 36 months underweight and short is seriously ill has mental apathy and no appetite The abdomen is usually distended Undigested food is passed in frequent bulky or loose stools Subcutaneous fat is first well preserved but lost later The muscles waste early Generalized edema is usually present but may be absent or slight in cases otherwise typical It is not due to cardiac or renal failure though the urine may contain a

(3) A N w York A ad Sc 57 722 733 1954

trace of albumin The hair becomes soft and straight usually loses pigment and is easily shed or pulled out of the scalp

Skin eruptions usually occur only terminally though not in all cases The only dermatosis peculiar to kwashiorkor is the enamel paint or erosive dermatosis In a few ad-



Fg 96—C l t kw b k ot pot b lly th l mb d p l h (Court y f T ow ll H C A New Y k Acad S 57 722 733 1954)

vanced cases deep flexural fissures which bleed and never look sodden appear in the armpit elbow back of the knee behind the pinna and at the angle of the mouth where they resemble angular stomatitis

In many cases of kwashiorkor the liver does not appear enlarged during life but almost always shows fatty infiltration In noninfected cases this begins first and disappears last at the periphery of the lobule Direct transition

from the fatty liver of acute kwashiorkor to frank cirrhosis has never been recorded Mortality is below 10% in uninfected cases

The most constant biochemical changes are marked reduction in serum albumin level in all pancreatic enzymes in plasma esterase and lipase in serum amylase cholesterase and alkaline phosphatase Blood urea total cholesterol and cholesterol esters are also reduced A protein rich diet produces a characteristic biochemical pattern of recovery

Histologic changes are found in all organs with a rapid turn over of protein (small intestine pancreas and liver) in exocrine glands and in many other organs including the endocrines especially the adrenals

Skim milk powder or calcium caseinate combined with a suitable form of carbohydrate is the treatment of choice Study of the effect of individual amino acids and vitamin B_1 is difficult in patients with severe cases for unless the patients receive skim milk protein they soon die Convalescent children have swollen abdomens thin limbs and pale hair (Fig 96)

[Are there readers who like the editor have repeatedly encountered the term kwashiorkor in the literature have come to realize that it is considered the prototype of nutritional liver disease in man and yet have but a hazy idea of the disease? If so this abstract is for you—Ed]

Nutritional Aspects of Cirrhosis in Alcoholism—Effect of Purified Diet Supplemented with Choline Gerald B Phillips and Charles S Davidson[4] (Harvard Med School) believe that one difficulty in the evaluation of diets and dietary supplements in chronic alcoholics with active liver disease is the rapidity with which these patients usually improve following hospitalization and consumption of even meager diets If it could be shown that these patients did not improve on a basic diet despite alcohol withdrawal and hospitalization but did improve on a more adequate diet it could be concluded that one or more constituents of diet were responsible

The authors studied five chronic alcoholics with active liver disease who were drinking heavily and eating poorly before hospitalization Complicating illness was encountered in only one in whom transient fever associated with moderate delirium tremens developed Four received

(4) Ann New York Acad Sc 57 812-830 1954

a purified diet of glucose and saline and one had glucose solution only While on the purified diet 4 10 days each patient consumed about 400 Gm glucose 4 Gm sodium chloride (except one patient) and 2 000-2 500 ml fluid daily Three had diarrhea which stopped a few days after dis continuing the purified diet In addition each received cho line orally daily It was discontinued at the end of the diet period in all but one patient

The purified diet was followed by one containing about 1 600 calories 50 Gm protein and about the same amount of salt and water daily as before In three patients caloric and protein intake was raised to about 3 000 calories and 75 Gm respectively for a subsequent period

Measurements of hepatic function and size made on admis sion were repeated at intervals Liver biopsies were per formed on admission and repeated serially on four

Active cirrhosis seemed to improve in two patients and worsen in three Although these three may have received a subtherapeutic quantity of choline two of them consumed as much or more choline a day as did the two who im proved Gastrointestinal absorption may have been insuffi cient since two of the patients whose liver disease became worse had diarrhea In one an episode of delirium tremens may have worsened the hepatic disturbance When these three patients received a more adequate diet their condi tion improved two having significant decrease in serum bilirubin after one or two days One or more constituents of the more adequate diet may have been responsible for mit igation of the active hepatic disease The factor does not appear to be choline alone in the amounts given but was not just calories as the more adequate diet was isocaloric with the purified diet

A striking feature of the histologic studies was the ap parent increase in fibrosis associated with recovery Al though this may have resulted from disappearance of fat and condensation of the remaining tissue the marked in crease in fibrous tissue argued for genuine progression of fibrosis The facts that the patient with the most hepatic fat had the least fibrosis and the one with minimal fat showed pronounced fibrosis do not suggest a relation of fibrosis to fat

Veno Occlusive Disease of Liver Derrick B Jelliffe Gerrit Bras and Kenneth L. Stuart[5] (Univ College of the West Indies Jamaica) report on a child with abdominal distention due to ascites and hepatomegaly jaundice and bilirubinuria Histologic examination at autopsy confirmed the diagnosis of veno occlusive disease of the liver

Veno occlusive disease has the following stages (1) Acute hepatomegaly develops suddenly in 5 10 days mainly in infants aged 18 months to 3 years often with ascites frequently following nonspecific upper respiratory tract infection often subsiding in 4 6 weeks (2) Subacute persistent firm hepatomegaly with or without recurrent ascites may occur spontaneously or after acute stage may subside clinically with high protein diet or pass into (3) chronic state of cirrhosis The histologic sequence is (1) acute exudative subendothelial intimal thickening with partial occlusion of the lumen in small and medium sized branches of the hepatic vein (2) centrolobular sinusoidal congestion (3) atrophy and loss of liver cell cords if the condition persists followed by (4) centrolobular and nonportal fibrosis

The cause of the disease is unknown It occurs in young Jamaican children who live mainly on carbohydrates Toxins bacterial or chemical may be important Malaria sickle cell disease and syphilis play no part Liver biopsies on 12 Jamaican children aged 3 11 with chronic cirrhosis revealed in 4 the features of chronic veno occlusive disease Cases have been reported from South Africa of senecio poisoning which were clinically similar to veno occlusive disease with widespread hepatic venous thromboses Sporadic cases of hepatic venous occlusion due to primary or secondary thrombophlebitis infections toxins neoplasms and congenital factors have been reported usually in adults as the Budd Chiari syndrome

Hepatic Blood Flow and Splanchnic Oxygen Consumption in Alcoholic Fatty Liver Bruce J Kessler John B Liebler Gerald J Bronfin and Martin Sass[6] (State Univ of New York) estimated hepatic blood flow in 17 normal men and in 12 alcoholic patients with fatty livers but without clinical signs of advanced cirrhosis Time interval be

(5) Ped t cs 14 334-339 Octobe 1954
(6) J Cl n. I vest 33 1338 1345 Octobe 1954

tween admission study and study at maximum improvement of the alcoholic patients was 21 116 days average 44 days

Liver biopsies done in conjunction with the estimation of hepatic blood flow in alcoholic patients shortly after admission revealed fat infiltration of varying severity in all cases At the time hepatic blood flow was restudied fat had almost completely disappeared from the liver of nine patients and minimal fat infiltration remained in three Increased minimal periportal fibrosis was observed in the biopsies obtained from 9 of 12 alcoholic patients

Although mean estimated hepatic blood flow for the group of alcoholic patients shortly after admission was lower than that for normal subjects the difference was not statistically significant When hepatic blood flow in the alcoholic patients before and after treatment was compared it was decreased in three and increased in nine

Mean hepatic extraction of bromsulfalein in the alcoholic group on admission was slightly lower than that in the control group After treatment the values were similar for the two groups Difference in mean bromsulfalein clearance between alcoholic patients and the control group was significant when first studied and insignificant after treatment

The average total oxygen consumption in the alcoholic patients before treatment was 167 9±9 8 ml /sq M /minute which was 19 5 ml higher than the average after treatment

Results of hepatic blood flow measurements indicate that fat infiltration in the liver of alcoholic patients does not result in impairment of total hepatic blood circulation In these studies the increase in splanchnic oxygen consumption was accounted for solely in the hepatic arteriovenous difference Average value for this difference was 65% greater in the initial test of the alcoholic patients than in the test following treatment

[It has been stated quite emphatically that fat in the liver impedes hepatic blood flow because the fat laden liver cells "obviously must impinge upon the sinusoids The validity of such oversimplified mechanistic concepts is clearly challenged by the results reported here —Ed]

Effect of Valsalva Maneuver on Portal Hypertension in Cirrhosis was investigated by Eddy D Palmer[7] (Walter

(7) Am J M Sc 2 7 661-662 J 1954

Reed Gen l Hosp) According to different authors the varices in portal hypertension rupture either from internal hydrostatic pressure or as a result of transmucosal erosion Palmer studied the portal venous pressure of 15 patients with biopsy proved portal cirrhosis during a sustained Valsalva maneuver

PROCEDURE —Esophagoscopy was carried out with the patient horizontal in the left lateral position The level of reference for the manometric zero point was the axis of the esophagus which is also

EFFECT OF VALSALVA MANEUVER ON PORTAL PRESSURE (MM WATER)

PATIENT	RESTING PRESSURE	MAX. PRESSURE ON VALSALVA (REPEATED IN SOME CASES)
1	460	660
2	245	510 485
3	420	525
4	420	600 610 585
5	390	505
6	280	410
7	510	660
8	485	550 575
9	425	590 590
10	310	515 480
11	495	600 610
12	305	490
13	510	665
14	390	640
15	455	625 660

the level of the right atrium when the patient is in this position Water was used as the balancing medium in the simple open manometric system After endoscopic measurement of extent and diameter of the varices resting intravariceal pressure was measured by inserting a needle into the most proximal varix of suitable diameter The patient was then directed to take a deep breath and to 'bear down as at stool Rise in level of the water column was noted until the effort was concluded by the patient s inability to hold his breath longer

The column regularly rose quickly and at an even rate through about the first two thirds of the Valsalva effort and then rose more slowly During the Valsalva maneuver the pressure in the varix rose as much as 265 mm water and regularly rose more than 150 mm (table) However the rises were the result of sustained effort A strain as brief as a cough caused a variation of only about 40 mm

It is not believed that these findings help clarify the mechanisms responsible for initiation of hemorrhage from varices

Evaluation of Rectum to Lung Ether Time Test in Shunt Operations for Portal Hypertension and in Liver Disease was made by Sheldon S Waldstein Bruce T Forsyth and Edward J Jahnke Jr[8] (Washington D C) Portal circulation may be studied by injecting ether vapor into the rectum above the region drained by the systemic veins It is rapidly absorbed into the portal venous system carried through the hepatic circulation vena cava right heart and pulmonary circulation and appears in the expired air in detectable amounts If there is no delay in absorption and if the systemic and pulmonic circulations are normal the elapsed time from instillation of the vapor to its detection in the exhaled air—the rectum to lung ether time (RLT)—may be considered proportional to the portal circulation time

The RLT was determined in 62 persons with liver disease and 24 controls In 25 patients having shunt operations for portal hypertension pressure within the portal or splenic vein was obtained during surgery before and after the anastomosis postoperatively they were followed by determinations of the RLT

TECHNIC—After 3 cc ether is vaporized by hot water to a volume of 200 cc a rectal tube i inserted 10 in above the anus When patency is confirmed by a small injection of air ether vapor is injected rapidly and the tubing clamped to prevent loss The subject then begins to breathe evenly and deeply and an observer smells the breath for ether The end point is fairly distinct Cramps and an urge for bowel movement are the only side effects and disappear within seconds

All tests were done two to four hours after a meal Values of 14 57 seconds were found in persons with normal portal circulation and liver function Values in persons with liver disease portal hypertension or both did not differ significantly from normal After shunt surgery no direct correlation between RLT and portal vein or esophageal varix pressure was found although for the group the decrease in RLT after operation was of the same magnitude as the decrease in the venous pressures When the test was repeated at intervals there was poor duplication in unoperated subjects after portacaval shunting RLT became more constant

After anastomosis the portal circulation is altered and

(8) G t t l gy 26 781 788 M y 1954

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After anastomosis the portal circulation is altered and

(8) 26 781 788 M y 1954

the liver is completely or partly by passed probably accounting for the regular reduction in RLT seen after shunt operations and the relative constancy of the time thereafter Large postshunt variations in RLT occurred in only two patients in whom the shunt failed It is concluded that the RLT test has little diagnostic significance but is useful for determining the patency of a portacaval or splenorenal anastomosis

[Some of the variations observed in this test may be caused by the method of instilling the ether vapor A rectal tube inserted 10 in above the anus may as fluoroscopic observation shows either advance into the lower sigmoid or double upon itself so that the opening of the tube is actually situated low in the rectal ampulla Furthermore any gas injected through such a tube may pass upward stay locally or pass downward in an unpredictable fashion The distribution of the gas and its sites of absorption should certainly affect the results of the tests. The authors suggest that the variability of the test in patients with normal portal circulation may be caused by the liver alternatingly storing and releasing blood there is little evidence that this occurs in man —Ed.]

Life History of Patients with Cirrhosis of Liver and Bleeding Esophageal Varices Marvin M Nachlas James E O Neil and Alexander J A Campbell[9] (Boston City Hosp) studied 102 known cirrhotics who had at least one gastrointestinal hemorrhage, of which esophageal varices were the proved cause in 62 and the presumptive cause in 40 (suggestive group)

Figure 97 illustrates the survival times in months both after diagnosis of cirrhosis and after the first hemorrhage The slopes are closely parallel between the proved and suggestive groups except that the prognosis is more favorable in the latter The steepness of the slopes during the first month reflects that (1) the diagnosis was first made in some patients just before death and (2) first hemorrhage takes the lives of many patients (42% of the suggestive group 69% of the proved group 59% of the combined cases) One year after diagnosis of cirrhosis 49% of the patients were alive whereas at a comparable time after first hemorrhage only 28% were living

Of the 102 patients 88 died and of these hemorrhage was the precipitating or causative factor in 84 Coma and exsanguination were almost equally divided as cause of death Hemorrhage was severe (indicating shock and the need for transfusion of more than 2 L blood) in over half the cases

(9) A n S rg 141 10 23 Janu ry 1955

Of the 56 patients with severe hemorrhage 17 died in coma after bleeding had ceased and 39 died of exsanguination Of the 40% surviving the initial hemorrhage only one third will die during the subsequent year and two thirds

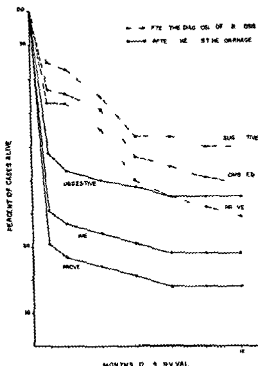


Fig 97—S rv l f p t ts ft d gnos f c h a d aft fi t h m h g (C urt sy f h bla M M et l A S g 141 10 3 J n ry 1955)

will be alive longer than one year Therefore any operation on these patients must carry a low mortality

Ascites and jaundice were absent in over three fourths of those who lived in patients who died ascites was present in three fourths and jaundice in one half The significance of hepatomegaly is obscure It does not indicate either poorer or more favorable prognosis

Although the life of the nonbleeding cirrhotic patient is

unquestionably being prolonged when hemorrhage does occur there is no evidence that nonoperative measures can prolong life There is no proof that a patient with esophageal varices who has never bled has the same poor prognosis as one who has bled

Blood Ammonia Experimental and Clinical Study in Abnormalities of Liver and Portal Circulation is reported by Joseph D Mann Jesse L Bollman Kenneth A Huizenga Turley Farrar and John H Grindlay[1] (Mayo Clinic and Found)

The bacteria of the intestine break down certain nitrogenous substances to form ammonia which enters the portal circulation and is converted to urea in the live Whenever the portal circulation by passes the liver and is diverted into the systemic circulation elevation of ammonia level in the systemic blood may result Such elevation has been reported in cirrhosis in man and in dogs with anastomosis between portal vein and vena cava (Eck fistulas) There is debate as to whether it is due solely to diversion of portal blood or whether concomitant liver damage is at least partly responsible

The authors found that in cirrhosis the blood ammonia concentrations tended to be higher than normal with some further increase in the case of hepatic coma In many patients with severe cirrhosis however values were still normal The level of blood ammonia was not exactly correlated with the degree of consciousness In one patient true coma preceded a significant elevation by 24 hours In another blood ammonia level did not appreciably change after portacaval anastomosis

Ligation of the portal vein or Eck fistula led to sporadic elevations of blood ammonia concentrations in dogs uninfluenced by various diets or antibiotics Feeding six Eck fistula dogs with a large meat meal resulted in increased blood ammonia 18 hours later with one becoming drowsy The next day blood ammonia levels returned to normal and the drowsy animal recovered uneventfully Antibiotics had no effect (Fig 98)

Increasing quantities of ammonium chloride given intravenously to normal and Eck fistula dogs raised the blood

(1) Gastroenterology 27 339-410 October 1954

ammonia concentrations of both However about twice the dose was required to produce the initial elevation in the normal animal When NH_4Cl solutions were instilled rectally almost the same values were obtained in one Eck fistula dog as when the intravenous route was used One Eck fistula dog which had a value of 27 6 µg NH_3 N/ml (normal 1 2 µg) had a mild convulsion but recovered well Symptoms of coma were absent in these animals

F 98—V riat on n bl d mm ia e t t on Eck fi t la d g (e n l s) d n rm l d g wh n bject d t p oced d eat d C se and t th t mal w vi g t b t wh blood w sampled (Court y f M J D t I G t oe t logy 27 339 410 O t b 1954)

The liver efficiently removed endogenous as well as experimentally infused ammonia from the blood in all animals The liver of a normal an Eck fistula and a portal vein ligated dog removed blood ammonia at a rate of 216 218 and 294 µg /kg /minute respectively To obtain a maximal degree of hepatic removal of ammonia about twice the arterial blood concentration was required in animals with proportionately diminished hepatic flow

These results confirm earlier observations that blood ammonia may be elevated when the portal blood is diverted

by an Eck fistula or by portal vein ligation The striking spontaneous variations in blood ammonia may reflect the degree of ammonia formation in the colon at the particular time the blood is sampled Similar mechanisms may obtain in human cirrhosis

Ammonium Tolerance in Liver Disease Observations Based on Catheterization of Hepatic Veins are reported by Laurens P White Elizabeth A Phear W H J Summerskill and Sheila Sherlock[1] (Postgrad Med School London) Simultaneous samples of blood from antecubital and hepatic veins were taken to evaluate the role of portal collateral circulation and of liver function in the control of blood ammonium levels To accentuate differences in ammonium content at these sites and to test patients ability to metabolize ammonium a standard dose of NH_4Cl was given orally

Six ammonium determinations, each timed from the start of the collection of blood until an aliquot was pipetted into the diffusion chamber were made on each sample the changing concentration was plotted and the value at zero calculated by extrapolation Observations on 21 subjects without hepatic disease supported Conway s conclusion that in the fasting subject without liver disease there is no measurable ammonium in the circulating blood and that what is measured as blood ammonium is really ammonium liberated from other substances after the blood is drawn The nature of these substances is unknown but adenosine may be one Whatever the source of ammonium liberation was very rapid and at three minutes most of the ammonium was present The level at three minutes after shedding of blood was therefore taken as the ammonium content of each specimen

The mean fasting blood value in the 21 controls was 0 79 µg ammonia N/ml In five cirrhotic patients values for portal venous blood obtained at laparotomy or from abdominal wall collaterals averaged 2 7 times those for peripheral blood

Four of five patients studied during the acute phase of viral hepatitis had elevated peripheral and hepatic vein ammonium levels In three especially after ingestion of

(1) J Clin In est 34 158 168 F b ua y 1955

NH_4Cl the level in hepatic exceeded that in antecubital vein blood suggesting that ammonium from the intestine passed through the damaged liver to the systemic circulation

Fasting ammonium values in peripheral and hepatic vein blood in 26 patients with cirrhosis and portal vein collateral circulation averaged 1 27 μ NH_4 N/ml After ingestion of NH_4Cl values at 30 minutes in peripheral vein blood rose to very high levels which far exceeded the concomitant rise in hepatic vein blood These large amounts must have reached the peripheral blood by portal collateral channels

In five patients neurologic disturbances were accentuated during the NH_4Cl test Such symptoms occurred only in patients in whom ammonium levels remained elevated for a considerable time There was no difference between normal and cirrhotic subjects in the ability to synthesize urea

[These studies show that abnormal liver function as well as portal collaterals contributes to elevated blood ammonia levels The conclusion reached by others that the collateral circulation is alone responsible cannot be reconciled with the freedom from cerebral symptoms enjoyed by patients with marked portal obstruction but essentially normal livers (Banti s syndrome) —Ed]

Postnecrotic Cirrhosis of Liver Study of 45 Cases is reported by Oscar D Ratnoff and Arthur J Patek Jr[3] (New York) The diagnosis in this series (60% women) was made by liver biopsy and/or autopsy Criteria included presence of broad fibrous bands separating areas of parenchymal hepatic tissue in which the lobular architecture was often relatively well preserved This was in contrast to the characteristics of Laennec s cirrhosis a diffuse fibrosis involving all lobules with disruption of the normal relationships within the lobules Fatty infiltration of the liver common in Laennec s cirrhosis was absent or minimal Usually the surface was very irregular because of protruding nodules of varying size

The illness began as if it were acute infectious hepatitis in 12 patients Six others had had an attack of acute hepatitis 5 12 years previously The clinical severity of the original hepatitis seemed to bear little relation to the later development of cirrhosis Thirteen patients (29%) were

(3) J Ch onl D 1 266 291 M rch 1955

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(2) J Clin Invest 34 158 168 February 1955

died within one month of the first episode and 13 within one year The most frequent causes of death as in other types of cirrhosis were cholemia gastrointestinal hemorrhage and infection

[A thorough analysis of postnecrotic cirrhosis such as this one has long been needed but it is somewhat disappointing that the over all picture and course are when all is said and done not so very different from those of portal cirrhosis In one type of postnecrotic cirrhosis which deserves more emphasis the regenerated liver nodules are able to maintain adequate metabolism but hepatic architecture is sufficiently distorted to cause portal hypertension Clinically the patient with this type of cirrhosis is often unaware of his disease and seems to be enjoying normal health until he suddenly suffers massive hemateme is —Ed]

Spontaneous Recovery from Hepatobiliary Disease with Xanthomatosis is reported by William S Haubrich and Salvatore M Sancetta[4] (Western Reserve Univ) Integumental xanthomatosis rarely accompanies long standing disease of the liver and its biliary system Even more unusual is reversal of the associated disturbance in lipid metabolism with complete recovery

Man 32 about 19 months before hospitalization because of skin rash and painless jaundice received intravenous injections as antisyphilitic prophylaxis Pruritic jaundice with watery and light stools developed eight months later and lasted two months A month later he received a series of penicillin injections followed by recurrence of the same type of jaundice A macular eruption predominant over elbows and knees appeared two months before admission The lesions beginning as minute pearly painful and pruritic pinheads appeared in successive crops later hardening and persisting as non tender nodules

Physical examination revealed circumscribed yellowish gray nodules 2 5 mm in diameter cattered over almost the entire body The scleras were deeply jaundiced Serum tests showed icterus index 64 cholesterol—total 845 mg /100 ml ester 319 mg alkaline phosphatase 48 King Armstrong units total fat 2 250 mg /100 ml and phospholipid 1 590 mg

Liver biopsy demonstrated distortion of the trabecular pattern of lobular architecture Parenchymal cells varied in size shape and staining quality foci of necrotic cord cells were pre ent and inspissated b le pigment was seen within and without the smaller bile canaliculi Primary xanthomatous biliary cirrhosis was diagnosed

Six years later the sl in was free fron xanthomas and blood values were normal

The one common denominator in the hepato hyperlipidemic relation is an obstructive phenomenon which may appear at any site between the ampulla of Vater and the finest radicles of the ductal system

(4) C st oent l gy 26 658 665 Ap l 1954

chronic alcoholics It is possible that in some patients an inadequate diet contributes to the development of postnecrotic cirrhosis There is no evidence that it is a syphilitic lesion

Abdominal pain was the commonest complaint being present in four of every five cases It was usually episodic and occasionally associated with bouts of jaundice and fever in eight it was severe One third of the patients had significant weight loss Anorexia and nausea were common and early weakness was experienced by some

Hematemesis occurred in one third of the patients If they survived the first hemorrhage they invariably bled again and usually repeatedly Esophageal varices found at autopsy in 22 of the 39 examined were demonstrated by x rays in 9 Hemorrhagic phenomena were common with bleeding from one or another site in 18 patients

In contrast to Laennec s cirrhosis icterus (present in 40 patients) was often an early symptom Seven patients had pruritus Swelling of the abdomen attributable to ascites occurred in about 90% Sixteen patients had vascular spiders and seven palmar erythema Dilated veins on the abdominal and lateral thoracic walls were observed in 15 The liver was palpable in 34 patients At autopsy it was usually either normal or diminished in size Twenty seven patients died after a period of so called cholemia identical with that in hepatic failure due to other causes

The serum globulin was elevated to 4 1 Gm /100 ml or more in 20 patients 4 of whom had levels up to 6 3 Gm /100 ml or higher In one patient it was 10 2 Gm /100 ml and electrophoretically about 50% of the total serum proteins was gamma globulin A normal serum protein concentration had been found in this patient five years before onset of symptoms Cephalin cholesterol flocculation determined in 29 patients was 3-4+ in 28 Alkaline phosphatase was over 9 units in 12 of 22 patients

Since postnecrotic cirrhosis is occasionally found at autopsy in patients who had no hepatic symptoms during life it is likely that in some cases it is not a fatal lesion Among the reviewed patients 29 survived for at least one year after onset of symptoms and 10 were alive at the end of five years Of 17 who had gastrointestinal hemorrhage 7

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(4)—Ga t oent 1 gy 26 658 665 Ap 1 1954

In this case the clinical picture and ultimate complete recovery were not those of either benign intrahepatic stricture or primary xanthomatous biliary cirrhosis Cutaneous xanthomas, hepatomegaly prolonged, painless pruritic jaundice and high levels of cholesterol and phospholipids in a clear serum were found Conspicuously absent were two features said to characterize primary xanthomatous biliary cirrhosis i e, almost exclusive occurrence in adult females and chronic remittent, progressive course resulting in hepatic failure and death

The spontaneous recovery from a situation ordinarily considered fatally progressive is noteworthy indicating that similar cases need not be considered hopeless particularly if a history of earlier viral hepatitis or contact with a potential hepatotoxin is obtained

Studies on Copper Metabolism XIII Hepatolenticular Degeneration, according to G E Cartwright R E Hodges C J Gubler J P Mahoney K Daum M M Wintrobe and W B Bean[5] involves disturbance in the metabolism of amino acids and copper Copper metabolism was studied in seven patients with Wilson s disease

The mean plasma copper level was 50 µg /100 ml compared with a mean normal value of 116 µg Mean value of the absolute amount of direct reacting copper in the plasma was 26 µg /100 ml compared with a mean of 8 µg in the normal group In six patients copper concentration in the spinal fluid was increased and the mean value was three times that of the controls Copper in the erythrocytes of eight was not significantly different from the normal

In general excretion of copper in urine was 4 30 times the maximal normal value Urinary alpha amino nitrogen excretion was increased in six of seven patients There was good correlation between this value and copper in the urine

In one patient with relatively early Wilson s disease amino acid excretion was not increased This has been observed once before in well advanced Wilson s disease

Copper concentration was increased in all tissues except the heart and was most marked in liver and brain stem It was 9 17 times that of the control value in the nervous system, including the spinal cord Patients with hepatolenticu

(5) J Clin Invest 33 1487 1501 November 1954

lar degeneration were in positive copper balance to the extent of about 0 56 mg copper/day/mg copper ingested

Potassium sulfide was given orally to form insoluble copper sulfide in the gastrointestinal tract thus counteracting absorption of copper Potassium sulfide increased copper content in the stools but not in the urine The over all copper balance changed from +0 43 to −0 14 mg /day/mg copper intake However administration of BAL casein hydrolysate and calcium versenate intravenously increased urinary copper excretion 300 900 μg /day (100 400%) Increase was greatest (mean of 501%) when BAL and casein hydrolysate were given simultaneously Calcium versenate orally did not significantly change excretion

Treatment consists of a high protein diet 20 mg potassium sulfide with each meal and 5 day courses of BAL (2 5 mg /kg twice daily) or casein hydrolysate every 10 days until maximum improvement occurs

The primary defect in hepatolenticular degeneration seems to be congenital inability to synthesize ceruloplasmin a globulin that normally binds 96% of plasma copper The low plasma ceruloplasmin content results in increased absorption of copper from the gastrointestinal tract Excessive amounts of copper are deposited in the brain and liver causing characteristic lesion Accumulation of copper in the kidneys leads to functional impairment in reabsorption of amino acids and peptides

[Wintrobe s laboratory has also reported low serum uric acid levels in Wilson s disease presumably the renal tubules cannot reabsorb uric acid efficiently —Ed]

Needle Biopsy of Liver IX Further Experiences with Malignant Neoplasm are reported by James Ward Leon Schiff Philip Young and E A Gall[6] (Cincinnati) In 111 of 1 000 patients needle biopsy of the liver showed neoplasm The needle aspiration method was used in 9 patients the Vim Silverman needle in the other 102 the transpleural approach in 99 the transabdominal in 12 Neoplasm was found in 72 patients by the former approach in 10 by the latter Of the 11 patients who had more than one biopsy the malignant lesion was found in one of two specimens in 8 in one of three specimens in 1 in both specimens in 1 and the results of two biopsies were negative in the other Several weeks later autopsy on the last

(6) Gast oe t l g 7 300 306 S pt mb 1954

patient revealed extensive hepatic metastases from a carcinoma of the colon

Hepatomegaly was present in all but three patients One third of the enlarged livers did not feel nodular and degree of smoothness or nodularity was not helpful in differentiating primary and metastatic tumors The biopsy specimen showed neoplasm in 76% of patients with nodular enlargement of the liver and in 71% of those who e livers

VALUE OF LIVER BIOPSY IN DIAGNOSIS OF MALIGNANT NEOPLASM OF LIVER (111 CASES)

	NO OF CASES	% OF TOTAL CASES
Confirmed clinical diagnosis	69	62
Revealed correct diagnosis	13	12
Failed to demonstrate neoplasm	24	21 5
Specimen inadequate	5	4.5

felt smooth Liver function tests performed in 56 patients revealed bromsulfalein retention in 90% increased zinc sulfate turbidity in 70% and elevated serum alkaline phosphate levels in 68%

Liver biopsy confirmed the clinical diagnosis in 62% of the patients and corrected an erroneous diagnosis in an additional 12% (table)

Experimental Studies of Gallstone Formation were carried out on hamsters by Joseph G Fortner[7] (Memorial Cancer Center New York) to evaluate the observations of Dam and Christensen—the finding of gallstones in 16 of 18 hamsters fed a cholesterol free and nearly fat free diet for at least 87 days

Three groups of 100 hamsters each were maintained on nearly fat free diets of different composition The number of animals with gallstones at death was as follows

Fat free diet added vitamin A and D	10
Fat free diet vitamin A no vitamin D	17
Fat free diet vitamin D no vitamin A	26

Seventy two hamsters fed balanced laboratory rations had no gallstones

The gallstones appeared to be composed principally of crystalline cholesterol which made up 48-93% of the stones mass

[In all the welter of investigation pertaining to cholesterol metabolism

(7) Surgery 36 932 940 November 1954

the origin of gallstones is quite neglected. It is intriguing that the hamster gallbladder forms stones when cholesterol is withheld rather than fed in excess —Ed]

Intracholedochal Hemorrhage was observed by Darrell A Campbell[8] (Ann Arbor Mich) in the following case

Man 63 had surgery for a bleeding obstructing duodenal ulcer The common duct was first opened and a small catheter threaded through it into the duodenum as a precautionary measure against damage to this structure during resection of the ulcer and closure of the duodenal stump On the fifth postoperative day blood mixed with bile came from the choledochotomy drainage tube Bleeding was copious and for a few days the patient was jaundiced The site of the gastrojejunal anastomosis was taken down in an effort to control the bleeding before it was noticed that all fresh blood was coming from the duodenal limb After an incision was made distal to the closed stump bright red arterial blood could be seen spurting from the ampulla of Vater The duodenum and the head of the pancreas were then reflected until with a catheter within the common duct the intrapancreatic portion of the distal common duct could be palpated Alongside this structure a pulsating vessel could be felt When this was encircled with deep sutures bleeding stopped

After three days fatal gastrointestinal bleeding occurred Autopsy showed *massive hemorrhage from a small ulcer in the anterolateral* wall of the common bile duct about 1 cm. from the ampulla which had eroded into the posterior superior pancreatico-duodenal artery

The close anatomic relationship between this artery and the retro and intrapancreatic portion of the common bile duct is constant and therefore the use of tubes in the lower end of the common bile duct should be well considered before they are left in this position

Consequences of hemorrhage into the biliary duct system so called hemobilia are (1) hemorrhage in general and (2) effects of complete biliary duct obstruction The latter usually is of short duration but sufficient to produce jaundice lowered prothrombin time and pain

Relation of Pancreas to Regulation of Blood Lipids Lester R Dragstedt James S Clarke Georgiana R Hlavacek and Paul V Harper Jr[9] (Univ of Chicago) report observations which indicate that the pancreas is intimately concerned in the regulation of blood lipid levels

Total blood lipid levels of dogs in good nutrition ranged from 600 to 900 mg /100 ml During prolonged fasting normal levels were maintained when stores of body fat were available After complete pancreatectomy serum lipids

(8) Ann S g 141 125 1 8 J y 1955
(9) Am J Phy 1 179 439 4 0 Dec mbe 1954

progressively decreased to levels of 500 mg or less A somewhat greater and more rapid fall often to 400 mg or less followed ligation of pancreatic ducts Both procedures produce the characteristic syndrome of lipocaic deficiency in some degree having in common the removal of pancreatic juice from the intestinal tract In contrast after subtotal pancreatectomy in which a 1 2 Gm remnant was left connected to the lesser pancreatic duct there was a striking elevation in lipid levels which reached 1 000 mg or more in all but 3 of 30 dogs and rose to 1 500 mg or more in 11 With the hyperlipemia a type of diabetes developed that required two to three times the amount of insulin required after total pancreatectomy however excellent nutrition was maintained for many months and the lipocaic deficiency syndrome did not occur

In 12 dogs subjected to partial pancreatectomy the part of the duodenum receiving the lower pancreatic duct was converted into an isolated sac which was drained exteriorly This total deviation of pancreatic juice from the intestinal tract reduced the lipid level to normal or subnormal values and abolished the high insulin requirement These changes could be reversed by reimplantation of the fistula into the duodenum Dogs with partial pancreatectomy in which pancreatic juice was excluded from the intestinal tract by occlusion of the pancreatic duct showed profound hypolipemia

Daily feeding of 200-400 Gm fresh beef pancreas corrected hypolipemia and even raised lipid levels above normal in insulin treated depancreatized dogs and in dogs with occlusion of pancreatic ducts The same amounts in normal dogs failed to raise lipid concentration above normal range The normal pancreas in situ would appear to restrain production of hyperlipemia by pancreas feeding This may be attributable to islet function since dogs with partial pancreatectomy and duct occlusion and those with total pancreatectomy responded in general with higher lipid levels than dogs with simple duct ligation and a larger amount of islet tissue remaining

It can be postulated that in normal animals the supply of lipotropic materials in the diet suffices for normal fat utilization in the liver with normal blood lipid levels when

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[Lipocaic is not dead!—Ed]

Technic of Secretin Test Normal Ranges obtained with this test on 123 patients without pancreatitis are presented by David A Dreiling[1]

METHOD—Patients take no food after the evening meal and the test is done the next morning A double lumen gastroduodenal tube is passed under fluoroscope control until the tip is at the ligament

CALCULATED RANGES (MEAN ±2 STANDARD DEVIATIONS)

	30 Min	60 Min	80 M
Total volume (cc)	62 153	102 223	128-272
Total bicarb (mEq)	9 0 13 6	14 1 21 5	16 8-24 9
Total amylase (units)		173-1,270	505 1 605

of Treitz The openings in the longer segment will then be in the duodenum those of the shorter segment in the stomach After intubation both outlets of the tube are connected to flasks and these to gentle suction When a nonturbid alkaline secretion is obtained a control collection period of 10 20 minutes is started

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Normal ranges obtained after stimulation with Lilly secretin are shown in the table Bicarbonate is determined by a volumetric gasometer The Somogyi method for blood amyla e is used on a 1 50 or a 1 250 dilution of the duodenal aspirate but the protein precipitation step may be omitted

Pancreatic response to secretin can be affected by lesions which obstruct the flow of secreted juice or which injure the secreting cells Tumors which obstruct the ducts

(1) J Mt S al Hosp 21 363 372 M Apr 1955

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progressively decreased to levels of 500 mg or less A somewhat greater and more rapid fall, often to 400 mg or less followed ligation of pancreatic ducts Both procedures produce the characteristic syndrome of lipocaic deficiency in some degree having in common the removal of pancreatic juice from the intestinal tract In contrast after subtotal pancreatectomy in which a 1 2 Gm remnant was left connected to the lesser pancreatic duct there was a striking elevation in lipid levels which reached 1 000 mg or more in all but 3 of 30 dogs and rose to 1 500 mg or more in 11 With the hyperlipemia, a type of diabetes developed that required two to three times the amount of insulin required after total pancreatectomy however excellent nutrition was maintained for many months and the lipocaic deficiency syndrome did not occur

In 12 dogs subjected to partial pancreatectomy the part of the duodenum receiving the lower pancreatic duct was converted into an isolated sac which was drained exteriorly This total deviation of pancreatic juice from the intestinal tract reduced the lipid level to normal or subnormal values and abolished the high insulin requirement These changes could be reversed by reimplantation of the fistula into the duodenum Dogs with partial pancreatectomy in which pancreatic juice was excluded from the intestinal tract by occlusion of the pancreatic duct showed profound hypolipemia

Daily feeding of 200-400 Gm fresh beef pancreas corrected hypolipemia and even raised lipid levels above normal in insulin treated depancreatized dogs and in dogs with occlusion of pancreatic ducts The same amounts in normal dogs failed to raise lipid concentration above normal range The normal pancreas in situ would appear to restrain production of hyperlipemia by pancreas feeding This may be attributable to islet function since dogs with partial pancreatectomy and duct occlusion and those with total pancreatectomy responded in general with higher lipid levels than dogs with simple duct ligation and a larger amount of islet tissue remaining

It can be postulated that in normal animals the supply of lipotropic materials in the diet suffices for normal fat utilization in the liver with normal blood lipid levels when

aided or potentiated by lipocaic from the pancreas In absence of or with impaired endocrine function of the pancreas the presence of pancreatic juice in the intestines causes hyperlipemia and a high insulin requirement Withdrawal of pancreatic juice from the intestines of dogs with impaired endocrine function of the pancreas causes hypolipemia decreased insulin requirement and fatty infiltration of the liver

[Lipocaic is not dead!—Ed]

Technic of Secretin Test Normal Ranges obtained with this test on 123 patients without pancreatitis are presented by David A Dreiling[1]

Method—Patients take no food after the evening meal and the test is done the next morning A double lumen gastroduodenal tube is passed under fluoroscope control until the tip is at the ligament

Calculated Ranges (Mean ±2 Standard Deviations)

	30 Min	60 Min	80 M
Total volume (cc.)	62 153	102 223	128 272
Total bicarb (mEq)	9 0 13 6	14 1 21 5	16 8 24 9
Total amylase (units)		173 1,270	505 1 605

of Treitz The openings in the longer segment will then be in the duodenum those of the shorter segment in the stomach After intubation both outlets of the tube are connected to flasks and these to gentle suction When a nonturbid alkaline secretion is obtained a control collection period of 10 20 minutes is started

Secretin (Lilly) 1 unit/kg body weight dissolved in 5 or 10 ml distilled water is injected intravenously slowly with barbotage and over at least two minutes Gastric and duodenal drainages are collected simultaneously in divided samples for 30 60 or 80 minutes Duodenal fractions are examined for pH volume bicarbonate concentration amylase concentration icterus index guaiac reaction and cytology Fluctuation of pH or a drop to less than 7 indicates gastric contamination and invalidates the secretin test

Normal ranges obtained after stimulation with Lilly secretin are shown in the table Bicarbonate is determined by a volumetric gasometer The Somogyi method for blood amylase is used on a 1 50 or a 1 250 dilution of the duodenal aspirate but the protein precipitation step may be omitted

Pancreatic response to secretin can be affected by lesions which obstruct the flow of secreted juice or which injure the secreting cells Tumors which obstruct the ducts

(1) J Mt Sinai H p 21 363 372 M Ap 1955

cause a decrease in volume flow Inflammatory lesions may affect not only volume but bicarbonate and enzyme secretions

Biliary flow responds to secretin as follows (1) normal ducts and gallbladder—bile initially present disappears from aspirate (2) gallbladder function absent—bile present throughout test (3) complete biliary tract obstruction—bile absent throughout test (4) partial common duct obstruction—bile disappears from aspirate in a cholecystectomized patient

New Method for Assay of Proteolytic Activity of Duodenal Fluid Compared with Other Methods in Study of Fibrocystic Disease of Pancreas (Mucoviscidosis) is described by Hugo Leubner and Harry Shwachman[2] (Harvard Med School) The method is simple and applicable to the routine laboratory The change in viscosity of a gelatin solution is measured as it undergoes digestion under standard conditions

METHOD—Proper collection of the specimen of duodenal fluid submitted for assay is crucial Analysis of the fluid is started immediately following collection if this is impossible it is kept in a freezer to preserve enzyme activity

An 8% solution of Knox gelatin in distilled water is prepared in a water bath at 38 C Two ml of this solution is placed in a test tube with a 10 ml serologic pipet One ml of 5% $NaHCO_3$ is added followed by 1 ml of the duodenal fluid dilution (1 3 000 in healthy children) A blank is prepared in a second tube with 1 ml water instead of 1 ml duodenal fluid dilution Digestion is carried out in the water bath at 38 C for 60 minutes Gentle shaking two or three times during the incubation period is advisable to maintain a uniform enzyme substrate mixture After incubation viscosities of the blank and the digestion mixtures are immediately determined in a 38 C water bath using the same viscosimeter Viscosity is measured in an Ostwald viscosimeter of 4 ml capacity standardized to a flow time of 32 seconds with distilled water at 20 C Viscosity time of the standard gelatin solution (4% pH 8 5 at 38 C) is 160 seconds when freshly prepared A phosphate buffer may be used instead of the $NaHCO_3$ solution If many determinations are made at one time it may be advisable to stop the reaction by placing the tubes in an ice bath then rewarming to 38 C before making the viscosity measurement

Activity is expressed by the formula of the reaction constant

$$k = \frac{1}{t} \log \frac{V}{T}$$

where V is viscosity at time zero taken as viscosity of blank

(2) P d t 15 135 142 F bruary 1955

I viscosity at time t t incubation time in minutes To express activity of duodenal fluid for 1 ml the value for K is multiplied by the dilution factor

According to this method the proteolytic activity of the duodenal fluid ranged from 0 to 4 8 in 20 patients with pancreatic insufficiency and from 47 to 118 in 10 patients with nonpancreatic disorders These results compared favorably with those obtained by the more elaborate Free Myers method The gelatin viscosity method provided a greater scale of activity and appeared more sensitive than the simple Andersen Early method which does not seem sufficiently quantitative to detect partial pancreatic insufficiency

Effects of Morphine on Serum Amylase and Lipase were studied in 41 patients by A Bogoch J L A Roth and H L Bockus[3] (Univ of Pennsylvania) Usually ¼ gr morphine sulfate was given hypodermically Venous blood was drawn before and ½ 1 1½ 2½ 3 4 and 5 hours after morphine injection In other cases blood samples were taken 1½ 2½ 4 5 and usually 24 hours after injection of morphine All patients fasted overnight and except for water took nothing until the test was completed

Serum amylase was determined by the Somogyi technic Values over 120 mg were considered abnormal Serum lipase was tested by the Cherry and Crandall modifications of the Loevenhardt method the upper limit of normal being 1 2 cc In three patients with cholelithiasis myocardial infarction and hyperthyroidism respectively morphine produced concentrations of serum amylase or lipase or both within the range of values obtained in primary acute pancreatitis (5 times top normal value) Eight additional patients presumed not to have pancreatitis had increased concentrations of amylase or lipase or both after morphine injection In these patients values were commensurate with diagnosis of pancreatitis but below the range considered pathognomonic of acute primary pancreatitis Hyperenzymemia was observed within 5 hours after injection and slight increases were noted as long as 24 48 hours

In 4 of 11 patients with pathologic increases in pancreatic serum enzymes after morphine the enzyme levels were still above normal 24 hours after injection Thus ante

(3) G [illegible] logy 26 69 708 [illegible] 1954

cedent morphine injection must be taken into account in interpreting pancreatic serum enzyme values

Evaluation of Provocative Blood Enzyme Tests Employed in Diagnosis of Pancreatic Disease was made by David A Dreiling and Alexander Richman[4] (Mount Sinai Hosp New York) Elevation of blood amylase level occurs early in acute pancreatitis and rarely persists more than 72 hours Minimal elevations however are not pathognomonic Increased values have been reported in various diseases as well as after codeine or morphine injection In most cases of chronic pancreatitis and pancreatic cancer fasting blood enzyme levels contribute little to the diagnosis

To make the amylase test more efficient different provocative tests were developed The level of the blood enzymes was studied at intervals for several hours before and after administration of drugs either singly or in combinations designed to produce one or more of the following effects on the pancreas (1) stimulation of the flow of pancreatic juice (secretin) (2) stimulation of the production of pancreatic enzymes (methacholine, bethanechol) and/or (3) blocking of the outflow tract of the pancreatic duct system (morphine)

METHOD —Drugs used were secretin 100 units morphine 15 mg methacholine 20 mg and bethanechol 5 mg Secretin was given intravenously the others subcutaneously Blood samples were drawn in the fasting state and at regular intervals after injection of the drugs Amylase was determined by a modified Somogyi starch hydrolysis technic

After morphine the blood amylase ro e in 2 of 13 control patients from 72 to 206 and from 65 to 180 mg /100 cc respectively Methacholine increased the amylase level in 4 of 16 controls Bethanechol administered to 12 control patients and 10 with pancreatic disturbances slightly increased the level in 3 in each group Secretin and morphine combined produced an amylase elevation in 1 of 17 controls The secretin methacholine combination evoked no alteration in 15 patients without pancreatic disease Secretin methacholine and morphine when used in combination caused elevations in 7 of 14 controls Among 12 patients with pancreatic disease positive changes were obtained in 3

(4) A M A A h I t M d 94 197 21 A g t 19 4

Results indicate that pancreatic secretagogues and sphincter tonic drugs singly or in combinations are capable of evoking small transient elevations in blood amylase levels in an unpredictable fashion in patients with and without pancreatic disease Because of this it seems impossible to establish criteria for the utilization of these responses in diagnosis of pancreatic disease and therefore the provocative blood enzyme tests are of little diagnostic importance These conclusions might be expected on theoretical grounds since the results of provocative tests depend on four independent variables sphincter of Oddi function patency of pancreatic ducts inflammation of secreting tissue and acinar destruction

[There appears to be no question that the administration of morphine may be followed by a rise in the serum amylase Since this happens unpredictably and irregularly in patients both with and without pancreatic disease the unreliability of the provocative blood enzyme tests is emphasized.—Ed.]

Use of Human Serum Albumin in Management of Acute Pancreatitis Experimental and Clinical Observations are reported by Daniel W Elliott Robert M Zollinger Richard Moore and Edwin H Ellison[5] (Ohio State Univ) Animal experiments were designed to answer three questions Is trypsin liberated systemically in significant quantities during acute pancreatitis? Does albumin inhibit this trypsin? Does albumin have other beneficial effects in pancreatitis?

Trypsin cannot be measured directly in the blood since it combines with and is inhibited by antifibrinolysin The levels of this inhibitor and of a substrate of trypsin (fibrinogen) provide indirect expressions of tryptic activity

Pancreatitis was produced in dogs by injecting the dog's own bile into the accessory pancreatic duct Immediately after the injection blood pressure fell 20 30 mm Hg Thereafter it fell more slowly and usually stabilized at 80-100 mm Hg at one hour At eight hours blood amylase levels were 2½ 5 times preoperative levels values were slightly higher in peritoneal fluid Lipase levels of blood were 4 10 times the upper limits of normal and in ascitic fluid were often twice the blood level

In six dogs induced pancreatitis was untreated the fall

(5) G t oe ter logy 8 563 587 Ap 1, 1955

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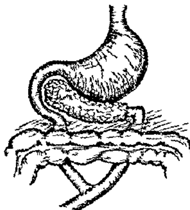
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(4) A M A Arch Int Med 94 197 21 Aug 1954

cm of its termination at the duodenum Since pancreatic juice can flow toward the tail of the pancreas as well as toward the head decompression of a pancreatic ductal system obstructed within the head of the pancreas can be achieved via the tail Surgery at the tail has a greatly lessened morbidity and mortality than a comparable procedure at the head

DuVal reports two cases in which direct anastomosis of the caudal pancreatic duct to jejunum en Roux Y was performed with no mortality minimal morbidity and no



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(C t y f D V l M K J A S g 140 775 785 D mb 1954)

complication No similar procedure has heretofore been described The anatomy after surgery is shown in Figure 99 Postoperative stool analysis indicated a significant improvement in fat digestion

Criteria for caudal pancreaticojejunostomy are (1) elevation of serum amylase and lipase during an acute attack (2) abnormal quantity of undigested fecal fat on a measured fat intake and (3) diminished duodenal output of amylase lipase and bicarbonate after stimulation of the pancreas by secretin and urecholine* In addition (4) on section of the pancreas at the junction of body and tail the pancreatic duct should be dilated (5) X ray study after injections of radiopaque fluid into the pancreatic duct system should

in antifibrinolysin and fibrinogen levels was half that in dogs given trypsin intravenously Average fall in plasma volume was 44% at eight hours in dogs given trypsin only 10% All dogs with untreated pancreatitis died in shock those given trypsin survived

Six dogs with pancreatitis given dextran intravenously had decreased antifibrinolysin and fibrinogen titers attributable to dilution of circulating plasma volume Four dogs survived In three dog with pancreatitis given a trypsin inhibitor the fall in antifibrinolysin titer was diminished however plasma volume deficit was 45% at 12 hours and all three dogs died

Concentrated human serum albumin without capacity to inhibit trypsin in vitro was given to 19 dogs in dose of 3 7 cc /kg at 1 8 and 24 hours after induction of pancreatitis Survival was in proportion to the doses given those dying having significant decreases in plasma volume

Five patients with acute pancreatitis were given 200 cc concentrated serum albumin daily to totals of 800 1 200 cc Plasma volume increased immediately after administration of albumin then diminished at 24 hours but rose to normal during several days of treatment As a rule antifibrinolysin and fibrinogen titers fell as plasma volumes expanded None of the patients died

Although trypsin appears to enter the blood early in pancreatitis it alone is insufficient to cause shock or death The beneficial effect of albumin is not trypsin inhibition but expansion of plasma volume This decreases antifibrinolysin and fibrinogen titers by a dilution effect

Caudal Pancreaticojejunostomy for Chronic Relapsing Pancreatitis is described by Merlin K DuVal Jr[6] (V A Hosp Bronx N Y) An attack of pancreatitis is almost always precipitated by stimulation of pancreatic secretion by food This observation appears to confirm the anatomic evidence suggesting pancreatic duct obstruction as the etiologic agent of chronic pancreatitis If pancreatitis is a manifestation of ob truction to the outflow of external pancreatic secretion then treatment should be directed at relief of the obstruction The site of obstruction is probably in or about the major pancreatic duct within the terminal 2 or 3

(6) Ann Surg 140 75 85 December 1954

METABOLISM



PHILIP K BONDY MD

not reveal egress of the dye into the duodenum (6) Stimulation of the pancreas by secretin should cause intraductal pressure to rise well above the resting normal

Administration of secretin under anesthesia resulted in a rapid rise in intraductal pressure to 490 mm water in the first case Over 30 minutes the pressure fell more than half way to normal with a final reading of 290 mm In the second case the pressure rose to 250 mm of water within five minutes from a resting pressure of 120 mm

[Attempts to clear the pancreatic ducts themselves by the technic here described or by an approach through the ampulla of Vater appeal as much more rational procedures than cutting a sphincter or draining a biliary tract innocent of stones or other disease —Ed]

PART VI

METABOLISM

THE THYROID GLAND

Quantitative Aspects of Iodine Metabolism Exchangeable Organic Iodine Pool and Rates of Thyroidal Secretion Peripheral Degradation and Fecal Excretion of Endogenously Synthesized Organically Bound Iodine Solomon A Berson and Rosalyn S Yalow[1] (V A Hosp Bronx N Y) assayed radioactivity after giving I^{131} and measured the concentration of protein bound iodine (PBI) in the plasma in 7 euthyroid subjects and 13 patients with Graves disease and estimated exchangeable organic iodine pool and rates of thyroidal secretion peripheral degradation and fecal excretion of endogenously produced organically bound iodine

The thyroidal secretion of organic iodine was estimated by analyzing the distribution of PBI^{131} in thyroidal and extrathyroidal compartments and the decrease in thyroidal radioactivity during inhibition with tapazole ® Daily secretion ranged between 83 and 175 µg in the euthyroid subjects *and between 183 and 925 µg in hyperthyroid* patients

Peripheral degradation of organic iodine was estimated from (1) urinary iodide secretion after administration of tapazole ® which was assumed to block thyroid uptake of iodine completely and (2) measurement of radioactivity of plasma after transfusion of exogenously biosynthesized labeled donor plasma protein bound iodine The rate of degradation was roughly proportional to the square of PBI in the plasma At normal PBI concentrations the biologic half life of biosynthesized organic iodine was 5 days but at concentrations characteristic of hyperthyroidism only 1½ days The estimated range of daily organic

(1) J Cl I t 33 1533 1552 N mbe 1954

and smoother than when the patient was awake Excursions tended to be smaller and more regular The BMR of euthyroid patients during sleep were within normal range Most of the patients had essentially the same BMR awake or asleep All nervous patients during sleep had a decrease in BMR to within normal range

Estimation of BMR during sleep eliminates one of the main sources of error in assessing thyroid function by use of oxygen consumption The BMR of euthyroid patients during sleep does not fall below normal standards and that of definitely hyperthyroid patients remains above normal range Ideally it should not be necessary to put patients to sleep to induce a basal state but it has often been difficult to obtain a reliable BMR with the patient awake There were no untoward experiences with pentobarbital sodium Patients given this drug are asleep not anesthetized The only serious disadvantage of the procedure is drowsiness and occasionally restlessness for the remainder of the day The reliability of the results probably justifies this inconvenience

Impaired Organic Binding of Radioiodine by Thyroid Following Radioiodine Treatment of Hyperthyroidism Richard H Kirkland[3] found a significant difference in the amounts of radioiodine discharged from the thyroids of control and of hyperthyroid patients treated with radioiodine when sodium thiocyanate was administered during an uptake study In 20 controls 96 6% of the trapped iodide was *organically bound representing an average loss of* 3 4% of trapped iodide following administration of thiocyanate In 10 patients previously treated with radioactive iodine for hyperthyroidism 45 9% of trapped iodide was organically bound representing an average loss of 54 1% of the trapped iodide following administration of thiocyanate It appeared that organic binding of iodide was impaired in patients treated with radioiodine signifying changes in thyroid function following isotope therapy This alteration was a specific effect similar to that produced by antithyroid drug or large doses of inorganic iodide

The thyroidal radioactive iodine uptake curves revealed distinct and characteristic changes The uptake progressed

(3) J Cl E doc 1 14 565 571 M y 1954

iodine degradation was 40 108 µg in euthyroid subjects and 260 2 600 µg in patients with Graves disease

The exchangeable thyroidal pool of organic iodine was the same in hyperthyroidism and euthyroidism but was reduced after antithyroid therapy The apparent extrathyroidal space of distribution of biosynthesized organic iodine averaged about 9 L Fecal excretion of organic iodine approximated 10 15% of the organic iodine which was degraded

Since hyperthyroid patients were found to degrade 7 9% of the total iodine pool daily complete blockage of iodine accumulation in the thyroid gland would lead to rapid depletion of the hormone and therefore to rapid remission of symptoms Doses of tapazole® large enough to block the thyroid completely are recommended for treatment of hyperthyroidism The dosage should be reduced only after the euthyroid state is attained

[Recent theoretical studies of thyroid function have been increasingly concerned with mathematical interpretations from which various potentially useful data may be derived This article is a good example of this type of work other authors who have published similar analyses include Brenner *et al* (Clin Sc 13 441 November 1954) Hickey and Brownell (J Clin Endocrinol 14 1423 November 1954) and Ingbar (ibid 15 238 February 1955) Unfortunately it is necessary to make certain basic assumptions in order to derive the mathematical equations on which these analyses are based Various authors start out with somewhat different axioms and end up therefore with somewhat different interpretations of their data For the moment little practical advantage is gained from these maneuvers however in the future extensions of this technic may permit routine quantitative determination of such important factors as rate of thyroxin secretion and degradation —Ed]

Basal Metabolic Rate during Sleep R Fraser and B E C Nordin[2] (London) gave pentobarbital sodium intravenously to 73 patients and amylobarbital sodium orally to 53 to induce sleep Basal metabolic rates were estimated before and after sleep was induced Depth of sleep varied from one patient to another but did not approach that in surgical anesthesia The rubber mouth piece was inserted before the patient went to sleep or occasionally during sleep At times the lips had to be held around it to prevent leakage

The tracing made during sleep was usually straighter

(2) La t 1 532 533 M 12 195

to protein bound I^{131} that portion of I^{131} which was taken up by the gland

The total clinical picture BMR I^{131} excretion thyroid uptake curves and chemical determination of organic iodine in the blood were reliable in judging effects of treatment of thyrotoxicosis Protein bound I^{131} level should be interpreted with caution in evaluating the status of treated patients

[The two preceding articles emphasize the difficulty of interpreting studies of I metabolism The situation in radioiodine treated hyperthyroid patients is similar to that following subtotal thyroidectomy (Blom and Terpstra 1954 55 YEAR BOOK p 591) although the mechanism may be different Radioactive iodine studies must be viewed with critical skepticism in patients who have received antithyroid treatment of any type even including surgery or radiation—Ed]

Clinical Value of TSH Test in Diagnosis of Thyroid Diseases George A Bishopric Norman H Garrett and William M Nicholson[5] (Duke Univ) measured change in the uptake of radioactive iodine induced by thyroid stimulating hormone (TSH) in 34 subjects Each received tracer doses of 10 20 μc radioactive iodine Estimates of iodine uptake were made by a scintillation counter over the thyroid 3 and 24 hours after the tracer dose was given Each subject was then given 4 USP units of lyophylized thyrotropic principle obtained from bovine anterior pituitary glands The tracer dose of I^{131} was repeated 24 hours later and the uptake estimated again after 3 and 24 hours The percentage differences between the two 3 hour uptakes and the two 24 hour uptakes were considered the measure of the functional capacity of the gland

In four normal subjects not receiving thyroid medication TSH produced a mean increa e of 34 5% in the 24 hour uptake of I^{131} with a range of 22 50% In 10 normal subjects who had been receiving thyroid medication the 24 hour mean increase in I^{131} uptake was 25 5% ranging from 10 to 50% Two normal subjects given iodine compounds for x ray studies showed no response to TSH In five patients with untreated primary hypothyroidism the response was only a 1 6% mean increase in the 24 hour I^{131} uptake In seven patients with primary hypothyroidism treated with thyroid medication the 24 hour uptake increased only an average of 1 3% Of six patients with hypothyroidism sec

(5) Am J M d 18 15 19 J y 1955

rapidly during the first one to two hours but reached its maximal point early so that after two hours there was no further increase In contrast in the normal curve the uptake was still progressing after three hours Under these circumstances the uptake is a reflection of the ability of the thyroid to trap serum iodide In the absence of organic binding the amount of iodide in the gland gradually falls in proportion to the urinary excretion The thyroid iodide serum iodide ratio is maintained constant until all iodide is excreted or until the block to organic binding is released

The iodide trapping mechanism is abolished by the presence of the thiocyanate radical

Blood Levels of I^{131} after Tracer Doses in Patients with Thyrotoxicosis Treated with Radioiodine G A Lindeboom Th E Hoogendijk Van Dort and J De Jong[4] (Amsterdam) examined 23 patients with thyrotoxicosis before during and after treatment with radioiodine and compared the clinical condition with the levels of I^{131} uptake protein bound I^{131} and BMR

In 7 of the 23 cases the protein bound I^{131} concentration was much higher during the euthyroid state than before I^{131} treatment In one patient the protein bound I^{131} was 5 2% 72 hours after tracer doses or more than 10 times the normal value three months after clinical cure In three the radiochemical signs of cure appeared several months after the signs of clinical cure In most cases however the protein bound I^{131} concentration diminished as the clinical condition improved although not at the same rate In all cases the values were above normal and in the thyrotoxic range at the time a clinical euthyroid state had become well established

The discrepancy between the clinical state and the protein bound I^{131} is difficult to explain There may be a correlation of these findings with the fact that thyroid remnants after thyroidectomy or I^{131} treatment remain hyperactive The measurement of protein bound I^{131} did not give quantitative values for the total protein bound iodine but only values related to the tracer doses The active remnants of the thyroid gland might rapidly convert

(4) Act m d sc d v 150 487 49 1955

the uptake is below 20% thyroid function is considered normal If it is above 20% a further course of 360 or 540 mg thyroid is given for one to two weeks and the uptake again determined Uptake of less than 20% at this level is highly suggestive of a euthyroid gland Above 20% it is strongly suggestive of thyrotoxicosis Radioactive uptake is determined by external counting over the thyroid 24 hours after a 50 μc tracer dose of I^{131}

The changes produced in thyroid I^{131} accumulation by increasing doses of thyroid are shown graphically in Figures 100 and 101 Of 55 euthyroid patients with goiters all had I^{131} uptakes below 20% when taking 180 to 540 mg thyroid daily In the thyrotoxic patient there was no appreciable suppression of I^{131} uptake even after 720 mg thyroid daily and in only one was the I^{131} uptake below 20%

The thyroid suppression test was considered most useful in patients with equivocal clinical or laboratory findings

[A somewhat similar method has been suggested by Werner and Spooner (Bull New York Acad Med 31 137 145 February 1955) using 70 150 μg triiodothyronine Both methods have been useful in a few cases we have studied —Ed]

Effectiveness of Triiodothyronine or Thyroxin Administered Orally in Treatment of Myxedema was studied in six patients who exhibited classic signs symptoms and metabolic derangements of myxedema by Herbert A Selenkow and Samuel P Asper (Johns Hopkins Univ) Daily oral administration of 70 105 μg l triiodothyronine or 150 200 μg dl triiodothyronine resulted in a return to clinical euthyroidism in 10 14 days All symptoms of hypothyroidism disappeared and there were no toxic effects Each patient lost 6 10 lb during the first two weeks and remained euthyroid for the duration of therapy

In one patient 200 μg daily of dl triiodothyronine as the free amino acid failed to restore the basal metabolic rate to normal levels whereas 300 μg daily was effective Euthyroidism was subsequently maintained with only 150 μg dl triiodothyronine hydrochloride daily It was not clear whether the discrepancy between the free amino acid and the hydrochloride form resulted from differences in absorption or from other causes Substitution of 300 μg sodium l thyroxin daily by mouth for 105 μg l triiodothy

(7) J Clin E doc ol 15 285 296 M b 1955

ondary to pituitary failure five had an increase in I^{131} up take after TSH (mean increase, 197%) and one with proved secondary hypothyroidism had a decrease

The change in 24 hour uptake of I^{131} by the thyroid gland after stimulation with a single injection of TSH was considered a reliable and valuable diagnostic aid in distinguishing between primary and secondary hypothyroidism and euthyroidism in patients who had been receiving substitution therapy which had suppressed thyroid function and in whom the clinical and laboratory results were otherwise similar

[*The dose of TSH used in this study was small This may account for the fact that one of the hypopituitary patients failed to have the expected response The single dose and 24 hour follow up period is a great convenience but further observations will be necessary to establish the reliability of the method —Ed*]

Method for Increasing Accuracy of Radioiodine Uptake as Test for Thyroid Function by Use of Desiccated Thyroid Monte A Greer and G Edward Smith[6] (Nat l Cancer Inst) differentiated thyrotoxic from euthyroid patients by using suppressive doses of exogenous thyroid hormone and measuring the effect on I^{131} uptake The test consists of measuring the I^{131} uptake then giving 180 mg desiccated thyroid daily for one to two weeks and finally redetermining the I^{131} uptake If after this dose

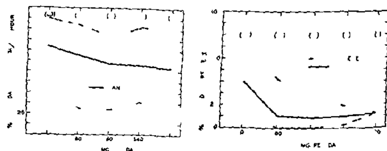


Fig 100 (left) —I uptake in 23 thyrotoxic patients treated with thyroid Numbers in parentheses refer to number of patients treated with each dose of thyroid
Fig 101 (right) —I uptake in 55 groups euthyroid patients treated with thyroid.
(Courtesy of Greer M A and Smith G E J Clin Endocrinol 14 1374 1384 November 1954)

(6) J Cl Endocrin l 14 1374 1384 November 1954

a single injection triiodothyronine appeared to be three to four times as potent as thyroxin On the basis of total calorigenic response thyroxin in doses over 10 μg/kg was more effective than equimolar doses of triiodothyronine

[Although l thyroxin may be more potent than l triiodothyronine in very large single doses at the therapeutic level (about 4 μg/kg in the adult) triiodothyronine is clearly much more potent These observations clarify the observations of Rawson *et al* (1954 55 YEAR BOOK p 573) which seemed inconsistent with the experimental data on animals —Ed]

Hypothyroidism and Thyroid Hyperplasia in Patients Treated with Cobalt Joseph P Kriss William H Carnes and Ruth T Gross[9] (Stanford Univ) observed hyperplasia of the thyroid in five patients who received enteric coated cobaltous chloride for anemia Three patients had visible goiters three had laboratory evidence of hypothyroidism and in one serious clinical myxedema developed The goiters and clinical and laboratory evidence of depressed thyroid function disappeared within several weeks after the drug was withdrawn

Boy 12 had received 32 transfusions in the previous five years for sickle cell anemia No goiter was present and thyroid function was within normal limits After he took 80 mg cobalt daily for nine weeks I uptake was 2% in 24 hours protein bound iodine was unchanged and serum cobalt level was 75 μg/100 cc A moderate sized diffuse goiter had appeared but there were no signs or symptoms of hypothyroidism Placebo tablets with the same enteric coating were substituted Four weeks later the I uptake had risen to 28% and the goiter was smaller Traces of cobalt could be detected in the serum 12 weeks after therapy had been discontinued A cobalt preparation from a different manufacturer 150 mg daily for five weeks reduced the iodine uptake to 12% in 24 hours The patient is receiving desiccated thyroid as well as cobalt to determine whether goiter formation may be prevented and if the hematologic response is influenced

The four other patients included a boy 4 who had received 60 80 mg cobaltous chloride daily for seven months He had a large nodular goiter was listless and lethargic and thyroid function was depressed Biopsy of the thyroid revealed marked hyperplasia A boy 6 after receiving 40 100 mg cobaltous chloride daily for 10 weeks had clinical signs of myxedema The thyroid gland was symmetrically and diffusely enlarged and biopsy revealed hyperplasia Thyoid function was greatly depressed A woman 55 with hypertension uremia and anemia was given cobaltous

(9) J A M A 157 117 1 1 J 8 1955

ronine in two patients produced no appreciable change in the clinical or metabolic status Thus the calorigenic effect of l triiodothyronine was about three to four times that of l thyroxin

It had previously been observed that patients who were euthyroid when receiving triiodothyronine parenterally had levels of serum protein bound iodine in the myxedematous range Oral administration of triiodothyronine produced similar results Thus the level of serum protein bound iodine in patients receiving triiodothyronine is not indicative of their metabolic status Athyreotic patients receiving l thyroxin had protein bound iodine levels at the upper limit of normal while they were otherwise euthyroid In previous reports athyreotic patients receiving desiccated thyroid had levels of serum protein bound iodine equivalent to their metabolic status

Calorigenic Effects of Single Intravenous Doses of l Triiodothyronine and l Thyroxin in Myxedematous Persons Charles M Blackburn William M McConahey F Raymond Keating Jr and A Albert[8] (Mayo Clinic) compared the effects of l triiodothyronine and l thyroxin in eight patients with myxedema Duplicate determinations of BMR were made daily A single injection of either triiodothyronine or thyroxin was given intravenously and the BMR followed until it approached preinjection level Triiodothyronine in doses above 4 µg/kg produced malaise restlessness aching anorexia and headache with doses over 10 µg these symptoms became intense Thyroxin in doses up to 50 µg/kg produced no subjective discomfort

After injection of triiodothyronine the metabolic rate rose more rapidly and to higher levels than after thyroxin However the metabolic effect of thyroxin lasted 70 90 days compared to 45 55 days for triiodothyronine With small doses l triiodothyronine produced a greater total caloric response than did equimolar amounts of l thyroxin whereas with large dosages thyroxin produced a greater total caloric response Thyroxin produced a greater and more sustained elevation of protein bound iodine

On the basis of the maximal metabolic rate produced by

(8) J Cl n I t 33 819 8 4 J 1954

ter) studied seven psychotic adult myxedematous patients with varying degrees of sensorial impairment justifying diagnosis of delirium Three were grossly myxedematous The degree of hypothyroidism in the others was varied In one it developed after treatment with radioactive iodine and in the other three it apparently rose spontaneously In all the predominant pre enting symptomatology was of the psychosis not of the hypothyroid state The clinical examination for delirium consisted of testing orientation remote and recent memory retention and recall serial subtraction and proverb orientation

Although all seven patients were psychotic they failed to demonstrate uniform behavior characteristics Three had an admixture of depressive and paranoid features two were depressed and anxious one showed an intensely manic reaction and one had bizarre somatic delusions and persistent symptoms of anxiety reaction Whereas in other forms of delirium the EEG waves increase as their frequency decreases in hypothyroidism and myxedema both slowing and lowering of the voltage were noted The particular disturbances of mood thought control and overt behavior varied greatly and did not correlate with the EEG The over all EEG changes are attributed to an impaired state of cerebral metabolism

In all cases clearing of the delirium and EEG improvement followed therapy indicating that when thyroid medication is given the cerebral metabolic defect is reversed The authors conclude that the psychosis of myxedema is basically a delirium not a specific reaction and as in cases of delirium from other causes follows no specific behavior pattern

[The importance of recognizing myxedema as a cause of psychosis is stressed in this and the preceding articles The variability of mental symptoms in myxedematous patients makes the diagnosis difficult on psychiatric grounds alone only the physician s healthy interest in physical as well as emotional factors can assure recognition of these curing a psychotics —Ed]

Four Year Study of Treatment of Hyperthyroid ... daily ...ore throat
Methimazole is reported by Jacqueline Chevalle[1] ... cell count
H McGavack Samuel Kenigsberg and Sidne... oin 69 Gm /
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(1) J Cl E doc 1 14 948 960 A gu t 1954

chloride 120 mg daily for three months No goiter was observed nor were there signs or symptoms of thyroid dysfunction Diffuse thyroid hyperplasia was found at autopsy A girl 3½ who had been receiving 40 mg cobaltous chloride daily for 3½ months had mild hyperplasia of the thyroid gland

The observed changes were regarded as toxic effects of cobalt It is concluded that cobalt is a goitrogenic agent Its indiscriminate use in infants and children should be avoided

Coexistent Myxedema Heart Disease and Psychosis was observed in two patients by Rowland J Calvert Eric Smith and Leslie G Andrews[1] (London)

CASE 1 —Woman 48 was hospitalized with orthopnea, anasarca cyanosis cardiomegaly hepatomegaly and a pulse rate of 62 She had dry skin patchy alopecia of the scalp and outer eyebrows brittle hair and a deep toneless voice A chest film revealed a classic myxedematous heart BMR was —19% and serum cholesterol 204 mg/100 ml Treatment was begun with thyroid substance 32 mg daily and after three weeks acute psychosis developed The dose was rapidly increased to 520 mg daily and after two days she became remarkably placid and rational Thyroid medication remained at 520 mg daily for three months and was then reduced to 200 mg because of flushes palpitation and excessive perspiration Her menses returned and she remained asymptomatic

CASE 2 —Woman 58 was hospitalized because of alternating semi coma and maniacal outbursts and a 17 year history of manic depressive episodes She had early congestive heart failure and myxedematous features resembling those in Case 1 Serum cholesterol was 400 mg/100 ml Thyroid substance 32 mg daily was begun and gradually increased to 200 mg a day The congestive failure cleared and her mental state improved She was able to continue normal activities on a maintenance dose of 130 mg

Myxedema may be difficult to diagnose Failure to recognize it as the basis for psychosis or congestive failure deprives the patient of the only beneficial treatment The large doses of thyroid substance especially in Case 1 deserve emphasis neither patient developed acute congestive cardiac failure or acute coronary insufficiency

Cerebral Metabolic Disturbances in Hypothyroidism Clinical and Electroencephalographic Studies of Psychosis of Myxedema and Hypothyroidism Thomas B Browning Robert W Atkins and Herbert Weiner[2] (Univ of Roches

(1) Brit M J 2 891 894 Oct 16 1954
(2) A M A Arch Int Med 93 938 950 June 1954

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(3) J Ch E docri 1 14 948 960 A gust 1954 The day after

was administered to 184 patients with *hyperthyroidism in* initial daily doses 15 and 60 mg and maintenance doses of 2 5 30 mg for periods varying from 14 days to 4 years Lugol s solution was added as the patients became euthyroid With adequate dosage improvement was observed in three fourths of the patients within the first week of therapy *Control of the thyrotoxic state required 2 26 weeks* 85% of all patients and 95% of those receiving large initial doses becoming euthyroid within 5 weeks

In 90 patients size of the thyroid was serially followed during treatment 12 showed an increase 45 a decrease and 33 *no appreciable change In 37 patients 35 with nodular* and 2 with diffuse hyperplastic goiters methimazole was used only preoperatively Of the remaining 147 96 were satisfactorily followed Of these 41 were still receiving methimazole 42 recovered completely (8 had recurrence) 7 were operated on and 6 were given radioactive iodine Toxic manifestations seen in 8 of the 184 included pruritus rashes edema urticaria fever and granulocytopenia

The highest *percentage of cures* was observed in patients under 35 In middle aged persons i e between 35 and 54 thyrotoxicosis was controlled less rapidly than in either the younger or the older persons Reduction in size of the thyroid was most consistently observed in patients aged 15 34 The authors conclude that *methimazole is a* rapidly acting relatively safe effective antithyroid compound

Large Doses of Propylthiouracil in Treatment of Hyperthyroidism were re evaluated by Elmer C Bartels and Martin M Kohn[4] (Lahey Clinic) *Doses of 600 1 000 mg* propylthiouracil daily were given to 24 patients with severe hyperthyroidism Half the patients had primary hyperthyroidism *the others adenomatous goiter with hyperthyroidism* A third had thyrocardiac disease For 5-64 days
ut received 1 000 mg propylthiouracil daily 1 with ade
tive c...ous goiter received 800 mg daily for 28 days then
Cereba daily for 94 days 12 received 600 mg daily for
Clinical a... s *Definitive therapy consisted of thyroidectomy*
of Myxeden... with primary hyperthyroidism receiving addi
Robert W A... l s solution for two or three weeks before sur

(1) Brit M J
(2) A M A Arch ... 14 1403 1415 ... 1954

gery and radioactive iodine in 3 with primary hyperthyroidism

Patients having adenomatous goiters with hyperthyroidism were more resistant to propylthiouracil than those with primary hyperthyroidism In 6 of the 12 with the former condition response was somewhat more rapid to higher doses than had been previously noted with smaller doses Four responded to higher doses after smaller doses had failed suggesting that all patients with hyperthyroidism respond to propylthiouracil if the dose is large enough and treatment long enough Patients with primary hyperthyroidism often responded dramatically to high dosages of propylthiouracil In two on the verge of crisis the improvement was especially rapid

Two of the 24 patients both with adenomatous goiter had side reactions In one mild urticarial skin rash developed after receiving 1 000 mg propylthiouracil for 49 days He was relieved by discontinuation of the drug and had no recurrence on 300 mg daily In the other diarrhea and fever developed after 10 days of 600 mg propylthiouracil daily In no instance was evidence of blood dyscrasia noted

Aplastic Anemia during Treatment of Hyperthyroidism with Tapazole ® Bennett Levine and David V Rosenberg[5] (Western Reserve Univ) reported a case of aplastic anemia during tapazole® (methimazole) therapy in which cortisone apparently hastened recovery

Woman 37 with a history of nervousness palpitations insomnia dyspnea fatigability and weight loss had slight exophthalmus a tremor and a diffusely enlarged thyroid gland The BMR was +43% and radioactive iodine uptake 75% in two hours Hemoglobin content was 71% and white blood cell count 7 100 Propylthiouracil 300 mg daily produced clinical improvement but was discontinued after a severe generalized urticaria developed White blood cell count was then 6 400 Lugol s solution 9 drops each day was begun but was discontinued after a month because of a macular lichenoid and scaly rash White blood cell count was 9 600 Tapazole® 20 mg a day was started and after two weeks increased to 40 mg daily After six weeks of tapazole® therapy she developed a sore throat and ulcerated lesions on the tongue The white blood cell count reached a low of 600 with 90% lymphocytes hemoglobin 6 9 Gm / 100 ml hematocrit 22% and platelet count 104 000 Serum bilirubin was elevated Bone marrow was hypocellular She was treated with streptomycin penicillin and oral doses of cortisone The day after

(5) A I t M d 41 844 848 O t be 1954

cortisone was begun the white count began rising and by the thirteenth day was 7 200 with 43% neutrophils Serum bilirubin became normal Hematocrit value did not change significantly until a transfusion was given She was discharged improved

The condition was diagnosed as aplastic anemia with a component of hemolytic anemia The rapid and dramatic clinical improvement suggested that cortisone hastened recovery although the patient might have recovered on conservative therapy alone

Untoward Hematologic Responses to Antithyroid Compounds Thomas Hodge McGavack and Jacqueline Chevalley[6] (New York Med College) after reviewing the literature report that every effective antithyroid drug has caused toxic reactions Aniline compounds thiobarbituric acid thiourea 2 thiouracil and thiazole compounds are clinically of no value as toxicity is too great compared with clinical effectiveness In effective doses methylthiouracil propylthiouracil and methimazole (tapazole®) are about equally toxic The most important reactions are severe granulocytopenia and agranulocytosis

The low toxicity previously ascribed to propylthiouracil was due to low dosages With doses of propylthiouracil of 100 150 mg daily granulocytopenia occurred in 0 1% of patients With larger amounts of the drug the incidence of granulocytopenia rose to 0 3% and mortality to 0 1%

Granulocytopenia occurred in 1% of patients taking methimazole compared to 0 3% for patients treated with propylthiouracil or methylthiouracil This figure is probably higher than the actual incidence of reactions to methimazole The higher the dose and the longer continued the greater the incidence of granulocytopenia The dose of methimazole is limited by the authors to 40 mg daily unless no antithyroid effect is noted in three weeks If a larger dose is required it is reduced as soon as improvement occurs

Granulocytopenia probably can be avoided by using the average effective dose of antithyroid compound increasing the dose only if necessary and decreasing dosage as soon as possible If the patient develops sore throat fever generalized aching rash or pruritus a blood count is immediately indicated If severe leukopenia is present the drug

(6) Am J Med 17 36-40 July 1954

should be stopped and penicillin and fluids administered

[Either propylthiouracil or methimazole may produce occasional toxic reactions The incidence of toxicity is higher with higher doses If the antithyroid drugs are used alone the required dose is considerably higher than is needed when iodine (e g Lugol s solution) is given simultaneously We have never seen a patient who needed the enormous amounts of propylthiouracil recommended by Bartels and Kohn (page 596) if Lugol s solution was given along with the goitrogen The advantages of accelerated response and reduced dosage tend to protect the patient against the toxicity of the antithyroid drugs when these are given combined with iodine —Ed]

Cortisone in Exophthalmos Report on a therapeutic trial of corti one and corticotropin (ACTH) in exophthalmos and exophthalmic ophthalmoplegia is given by a panel appointed by the Medical Research Council [7] The 28 patients treated (one twice) were aged 22 79 and consisted of 10 men and 18 women Thyrotoxicosis was present in 15 or 53% at start of treatment Exophthalmos was graded as slight moderate or severe depending on clinical findings as well as on exophthalmometer recordings There were four patients with slight exophthalmos none of whom had chemosis Ten of 20 with moderate and all of 5 with severe exophthalmos had chemosis Ophthalmoplegia was present in 19 patients 12 of whom had chemosis Of the patients without ophthalmoplegia only three had chemosis Patients who had chemosis usually had more severe paralysis of eye muscles than did the others

Results with cortisone 100 200 mg daily or ACTH 25 100 mg daily were disappointing Only three patients had marked improvement in exophthalmos and five slight temporary improvement In three the exophthalmos increased slightly during therapy Improvement in chemosis was the most constant response occurring in 15 of 19 patients The group whose proptosis was unaccompanied by chemosis and edema and who were without ophthalmoplegia showed the least response to treatment Of those whose thyrotoxicosis was reduced by antithyroid drugs about one half had improvement in proptosis coinciding with the decrease in thyroid function

It is suggested that the doses of cortisone and corticotropin used were inadequate and that further trials be conducted using higher doses

[These observations the most extensive yet reported suggest that the

(7) La t 1 6 9 J 1 1955

early claims of dramatic response to cortisone may have been overoptimistic Our limited experience confirms the findings reported here that, whereas chemosis and periorbital edema may be improved by cortisone the proptosis and course of the disease are not usually significantly affected —Ed]

Cancer of Thyroid William V McDermott Jr, Winfield S Morgan Edward Hamlin Jr and Oliver Cope[8] evaluated 190 proved cases seen at Massachusetts General Hospital between 1931 and 1951 Of 45 patients with follicular carcinoma 10 were males 35 were females of 89 with papillary carcinoma 26 were males of 45 with undifferentiated carcinoma 20 were males and of 11 of miscellaneous types of thyroid carcinoma 4 were males and 7 females Of the 89 with papillary carcinomas 28 had pre existing goiters for three years or more 54 had regional and 7 distant metastases and 88% were considered resectable Of the 45 with

CANCER OF THE THYROID
CUMULATIVE SURVIVAL RATE

CUMULATIVE SURVIVAL RATE IN PERCENT

PAPILLARY CARCINOMA

FOLLICULAR CARCINOMA

UNDIFFERENTIATED CARCINOMA

YEARS AFTER INITIAL ADMISSION

Fig 10 Cumul t v l te thy d c c l y h tol g c c a fic tion plotted logar thmically C ve ha th ame l i all pe ods hav g eq l period s rvival t s reg dle of cum l t ve survi al rate t g n per od (C rt y of McDerm tt W V J t al J Cl E doc l 14 1336 1354 N ember 1954)

(8) J Cl End cr l 14 1336-1354 N vembe 1954

follicular carcinomas 27 had pre existing goiters for three years or more 8 had regional and 20 distant metastases and 75% were considered resectable Of the 45 with undifferentiated carcinomas 10 had pre existing goiters for three years or more 18 had regional and 23 distant metastases and 27% were considered resectable

In papillary carcinoma comprising almost half the total series the cumulative survival rate was highest (Fig 102) and distant metastases were rare Regional lymph nodes were involved early Unlike the other conditions papillary carcinoma occurred in all decades with a relatively high incidence in the earlier decades and occurring even before puberty but mortality was distinctly greater after age 50

All thyroid cancers with a microscopic follicular pattern were classified as follicular The sex ratio was more than 3 1 female to male Almost two thirds of the patients had pre existing thyroid disease Follicular cancer probably represented two separate types of biologic behavior as indicated by the biphasic curve in the cumulative survival rate (Fig 102) One type invaded regionally and the patient had a short life span if it was not eradicated in the early stages The other type showed benign local and distant metastases that eventually proved fatal

Prognosis for patients with undifferentiated cancer of the thyroid was poor In les than a year after diagnosis 70% died

Significance of Solitary Nontoxic Thyroid Nodules Preliminary Report John B Vander Eugene A Gaston and Thomas R Dawber[9] (Framingham Mass) observed 5 234 persons believed to represent an unbiased sample for thyroid disease All subjects were examined once 75% twice and 17% three times The population of the community totaled 28 000 and by random sampling the names of 6 535 persons aged 30 59 were drawn Of these 4 494 co operated and 740 volunteers outside the sample group were included This was therefore an epidemiologic study of the incidence of thyroid nodules in an unselected normal population All were clinically free from arteriosclerotic or hypertensive heart disease

The incidence of nontoxic nodules on the basis of those

(9) N w E gl d J M d 251 970 973 Dec 9 1954

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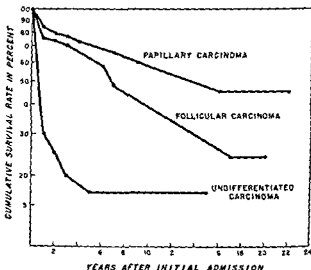


Fig 102 —Cumul t ur i l te n th oid anc r by h stolog cl s fi t on plotted l ga ithm cally t e ha the ame l pe n all pe ods h ng eq l pe iod survival rate g di f cum l t e urvi l ate at g en per od (C urt y of McDerm tt W V Jr t al J Clin E docr ol 14 1336 1354 N ember 1954)

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of colloid-containing thyroid acini showing evidence of hyperplasia Though it was impossible to diagnose thyroid carcinoma in the specimen the cellular irregularity was greater than is usually seen in simple hyperplasia

X ray study of the chest showed widespread mottling of innumerable small metastases throughout both lungs but no other metastases were found elsewhere and x rays of the skeleton revealed no abnormalities

A tracer dose of radioactive iodine was given of which 43% was excreted in 48 hours but the greatest uptake in the neck reached only 10% As tracer studies revealed that effective ablative doses of radioactive iodine would be prohibitively high treatment with thyroxin was begun in hope that the metastases like nodular goiter might slowly regress Sodium 1 thyroxin was started on July 16 1952 in a dose of 0 1 mg daily which was slowly increased until by October 7 she was receiving 1 mg daily with production of signs of mild toxicity The dose was reduced to 0 7 mg daily at which level no symptoms were produced and she was rehospitalized for further tracer studies On December 15 99% of an intravenous tracer dose was excreted in 48 hours without demonstrable uptake in either the chest or the neck Thyroxin was then discontinued and four weeks later typical signs of hypothyroidism developed The uptake of radioiodine in the chest reached 26% of the dose at 24 hours with no demonstrable concentration elsewhere

Suppression of iodide uptake after treatment with thyroxin parallels that observed in healthy persons in both degree and duration It was followed by a phase of rebound hypothyroidism as in healthy persons It is reasonable to suppose that the mechanism lies in suppression by the administered hormone of the pituitary output of thyrotropic hormone and resultant diminution in activity of the thyroid gland

[This observation is of the greatest importance It casts doubt on the validity of the argument that nodules disappearing under thyroid treatment are benign (an extension of the observations of Greer and Astwood 1954 55 YEAR BOOK p 598) It supports strongly the therapeutic regimen suggested by Sturgeon *et al* (1954 55 YEAR BOOK p 606) consisting of suppression of endogenous TSH between doses of I by large doses of desiccated thyroid. It raises questions about the validity of observations on the effect of a variety of treatments for thyroid cancer in which the concomitant dose of desiccated thyroid was not controlled. And most important, it offers a new treatment for patients with disseminated thyroid cancer —Ed.]

Menstrual Pattern in Hyperthyroidism and Subsequent Post Therapy Hypothyroidism Ralph C Benson and Morris E Dailey reviewed histories of 274 premenopausal women with hyperthyroidism treated at the University of

(2) *S g Gyn ec & Ob t 100 19 26 J uary 1955*

found in the first examination was 1 6% for the entire sample with 0 7% for men and 2 7% for women Subsequent examination over a five year period revealed single non toxic nodules in 19 men and 80 women an incidence of 1 9% Single nontoxic nodules were suspected in an addi

HISTOLOGIC FINDINGS IN SINGLE NONTOXIC ADENOMAS SURGICALLY REMOVED

HISTOLOGIC DIAGNOSIS	MALES	FEMALES	TOTALS
Colloidal adenoma	4	16	20
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Hashimoto s disease		1	1
Parenchymatous adenoma		2	2
Totals	5	23	28

tional 7 men and 53 women increasing the prevalence to a maximum of 3% Twenty eight single nodules were sur gically removed none were considered malignant by the examining pathologist *(table)*

Most of the nodules had an average diameter of 1 cm some were larger but few were over 3 cm Many would have been missed in the usual physical e amination In almost every case the patient was unaware of the presence of a mass Women with single nodules predominated over men in a ratio of about 5 1

[Only by the application of epidemiologic technics such as these can we hope to obtain accurate data as to the incidence and significance of thyroid nodules (see the 1954-55 YEAR BOOK pp 600-606) *This study is worth following as it unfolds over the next few years* —Ed]

Metastatic Carcinoma of Thyroid Successfully Treated with Thyroxin is reported by H W Balme[1] (St Bartholomew s Hosp London)

Woman 40 was first seen at age 19 with a painless lump in the right side of the neck At 25 a second smaller lump was noted nearer the midline on the same side Slowly increasing dyspnea on exertion was first observed at 29 and at 32 x ray study of the mass revealed widespread mottling throughout both lung field The mottling slowly progressed during succeeding years and at 36 the first lump was excised Histologically it consisted of apparently normal thyroid tissue *The second lump was excised and showed the same histologic picture* Because it seemed probable that the lumps represented local metastases of carcinoma of the thyroid total thyroidectomy was done but no neoplastic focus could be identified in the excised gland The patient was referred for radiotherapy A year later a third nodule was removed from the neck It was composed

(1) Lancet 1 812 813 Apr 17 1954

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Two other studies were made on a woman lacking both ovaries and adrenals In the first study all hormone therapy was withdrawn for 48 hours before and 24 hours after intravenous administration of a tracer amount of hydrocortisone permitting evaluation of the metabolism of the homone when the tissues of the recipient were depleted of this substance In the second study performed while she was receiving 100 mg hydrocortisone daily by continuous intravenous infusion the infusion was interrupted for a half hour while a tracer dose was given No difference in the fate of the two tracer doses was apparent

In all studies over 90% of the radioactivity administered was excreted in the urine and feces within 72 hours There was no evidence of in vivo breakdown of the hormone as determined from measurements of expired carbon dioxide No radioactivity was found in the spinal fluid of one patient eight hours after intravenous injection of the hormone Within 24 hours from 70 to 80% of the hormone was eliminated in the urine in the form of conjugated metabolites at the rate characterized by an average half life of 3 6 hours This rate and the cumulative excretion were independent of the amount of hormone injected and the physiologic or pathologic status of the patient

The rapid metabolism of hydrocortisone was demonstrated when the unaltered hormone accounted for only 10% of the blood radioactivity within 15 minutes after completion of intravenous infusion

Blood and Pituitary Adrenocorticotropin in Adrenalectomized Rats with Hypothalamic Lesions S M McCann and Katherine L Sydnor[4] (Univ of Pennsylvania) produced lesions in the hypothalamus of adult male rats by destroying the median eminence of the tuber cinereum Bilateral adrenalectomies were later performed Depletion of adrenal ascorbic acid was an index of ACTH activity If the hypothalamic lesion was effective adrenal ascorbic acid was not depleted All the rats were maintained on desoxycorticosterone acetate chow ration and horsemeat Fourteen days after adrenalectomy they were anesthetized and bled and assays made of ACTH in the blood and in the anterior pituitary

(4) P oc Soc E per B l & M d 87 369 373 N embe 1954

California hospital during 15 years Of these 144 had Graves disease 77 had toxic diffuse goiter without exophthalmos 33 had toxic recurrent goiter and 20 had toxic nodular goiters

Of 221 patients with diffuse toxic goiter or Graves disease amount and duration of menstrual flow was reduced in 130 unchanged in 81 and increased in 10 Similar findings were recorded in patients with toxic recurrent and toxic nodular goiters Amenorrhea before therapy was noted in 21 patients all with exophthalmos and toxic diffuse goiters In 27 onset of hyperthyroidism was during pregnancy Successful medical or surgical therapy of the toxic goiter was usually followed by resumption of normal menstruation After hyperthyroidism was treated clinical hypothyroidism appeared in 31 patients (14%) Of these 18 had menorrhagia or polymenorrhea Most had previously had oligomenorrhea with hyperthyroidism None had any decrease in the menstrual flow during low thyroid function Normal menses usually reappeared after one or two months of desiccated thyroid therapy

The thyroid gland may influence the ovary indirectly via the pituitary gland although the general metabolic effect of thyroid hormone probably is also important

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THE ADRENAL GLANDS

Fate of Hydrocortisone 4 C^{14} in Man The dynamics of distribution and excretion of labeled hydrocortisone was studied in four patients by Leon Hellman H Leon Bradlow Jerome Adesman David K Fukushima J Lawrence Kulp and T F Gallagher[3] (New York) A man and a woman each received a tracer quantity of hormone approximating 0 25 mg on another occasion the same amount of labeled hydrocortisone and 100 mg carrier hormone were given to the same man This experiment permitted evaluation of the effect of the quantity of hormone given on its subsequent fate in the individual

(3) J Clin Invest 33 1106-1115 August 1954

The others showed no abnormality except for a higher glucose level in the mental retardation group Eosinophil responses to ACTH differed significantly only in the group with congenital adrenal hyperplasia as compared to the normals The eosinophil response to epinephrine was the same in all groups The children with congenital adrenal

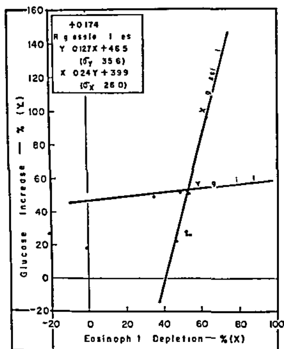


Fig 103—Comp so f eos oph l d gl ose ponses to ep phrin (Court y f Ely R S et l J Cl I est 33 1 87 1593 December 1954)

hyperplasia responded to epinephrine and to ACTH differently as measured by the decrease in eosinophil count

The hyperglycemic response to epinephrine was greater than to ACTH and greatest in the children with congenital adrenal hyperplasia The 17 OH corticosteroid response to ACTH was abnormal in children with congenital adrenal hyperplasia mental retardation and convul ive dis

Normal rats had adrenal ascorbic acid depletion after unilateral adrenalectomy After total adrenalectomy and with the stress of anesthesia and exsanguination ACTH content of the blood was 11 μ/100 ml and total ACTH content of the pituitary was 215 μ Rats that had lesions rostral to the median eminence of the tuber cinereum reacted to the stress of anesthesia and exsanguination to the same degree as normal rats These rats did not have diabetes insipidus and the adrenals were of normal size If the median eminence was incompletely destroyed ascorbic acid depletion occurred but concentration of ACTH in the blood was about 5 μ/ml and in the pituitary about 108 μ Rats with effective lesions of the median eminence showed no adrenal ascorbic acid depletion and had severe diabetes insipidus Blood ACTH was not detectable after stress Serial sections of the brains demonstrated interruption of the supraopticohypophysial tract either in the median eminence or just rostral to it The adenohypophyses were normal histologically in three cases examined Lesions that failed to produce diabetes insipidus also failed to influence blood ACTH levels

Lesions of the hypothalamus effective in preventing an ACTH reaction to stress interrupted the supraopticohypophysial tract as proved by development of diabetes insipidus and by histologic sections

[*The close relationship between diabetes insipidus and the control of adrenocorticotropin secretion is surprising and may be coincidental These studies underline our ignorance of the mechanisms controlling ACTH secretion —Ed*]

Studies of 17 Hydroxycorticosteroids V Responses of 17 Hydroxycorticosteroids Eosinophils and Glucose to ACTH and Epinephrine Robert S Ely Patrick F Bray Richard B Raile and Vincent C Kelley[5] (Univ of Utah) compared fasting blood levels of eosinophils glucose and 17 OH corticosteroids with the levels after ACTH and epinephrine administration in 156 children There were 40 normal children 6 with congenital adrenal hyperplasia 25 with rheumatic disease 29 with mental retardation and 56 with convulsive disorders Those with congenital adrenal hyperplasia had significantly higher eosinophil counts and lower glucose and 17 OH corticosteroids than normal

(5) J Cl Invest 33 1587 1593 December 1954

tention was not encountered in any patient studied probably because glucose in water was used rather than saline as the diluent

Fluorohydrocortisone and Chlorohydrocortisone Highly Potent Derivatives of Compound F Metabolic and therapeutic studies of chlorohydrocortisone and fluorohydrocortisone by Alan Goldfien John C Laidlaw Najib Abu

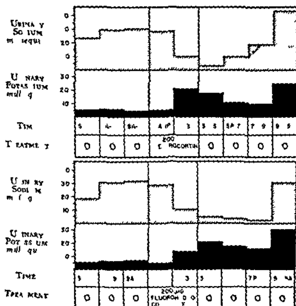


Fig 104 Effect f t e 1 dmn t d el roc t nd fluo hyd ocortison on n y sod m d pot m n m 3 w th Add son d ea m t d on nt d t (p d g 1 7 Eq od m d 118 mEq pota m d 1) (Cou t y f Goldfien A 1 New Engl d J Med 5 415 4 1 Ma 17 1954)

Haydar Albert E Renold and George W Thorn (Harvard Med School) indicate that a chlorine or fluorine atom at the 9 alpha position of hydrocortisone potentiates the metabolic activity and prolongs the action of the cortisone Fluorohydrocortisone is more potent than chlorohydrocortisone

Both compounds were successful as the sole maintenance therapy of patients with Addison disease Fluorohydro

(7) New Engl d J Med 5 415 4 1 M 17 1955

orders. In none was there any steroid response to epinephrine.

When simultaneous eosinopenic and steroid responses to ACTH were compared in 128 children, excluding those with congenital adrenal hyperplasia, no significant correlation was found. Comparison of simultaneous eosinopenic and hyperglycemic responses to epinephrine in 61 children also showed no significant correlation (Fig. 103).

The 17-OH corticosteroid response to ACTH is considered the most valid of the tests as a criterion of adrenal cortical function.

Clinical Uses of Intravenous Hydrocortisone. J. Max Kukes, Richard H. Orr and Peter H. Forsham[6] (Univ. of California) listed acute adrenal crisis, panhypopituitarism, functional adrenal insufficiency after corticosteroid therapy and shock unresponsive to usual therapy as logical indications for intravenous administration of hydrocortisone, available in 20 cc. ampules of 100 mg. free hydrocortisone in 50% alcohol.

CASE 1.—Man, 52, with x-ray signs of ulcerative colitis, was treated with cortisone acetate, 100 mg. daily, and then hydrocortisone orally, 160 mg. daily, without improvement. Colectomy was planned and stepwise reduction in hydrocortisone and decreasing dosages of ACTH begun. The last hydrocortisone was given two months and the last ACTH one week before surgery. During surgery, shock developed which was unresponsive to blood transfusions or intravenous injection of vasopressor agents but promptly responded to a slow intravenous drip of 100 mg. hydrocortisone in 1,000 cc. 5% dextrose in water. Normal pressure was maintained throughout the operation and postoperatively.

CASE 2.—Man, 60, who had undergone total gastrectomy and esophagojejunostomy for a large gastric ulcer and hiatus hernia, was admitted for revision of the esophagojejunostomy. During surgery the pressure fell despite multiple blood transfusions and intravenous and intramuscular injection of vasopressor agents. Intravenous hydrocortisone was started, which successfully maintained the blood pressure during and immediately after the operation.

These cases demonstrated the value of intravenous hydrocortisone in acute adrenal insufficiency after adrenal suppression and as a potentiating agent for vasoconstrictors. Other indications cited were fulminating allergic and toxic reactions. Intravenous infusions up to 50 mg./hour have been given with no ill effect. Excessive sodium re-

(6) Metabolism 3:481-499, November, 1954.

ney one an embryonal cell carcinoma of the testis and one an adenocarcinoma of the breast

Woman 48 hospitalized with metastatic carcinoma of the breast underwent bilateral adrenalectomy and was adequately maintained on 2 mg cortisone acetate daily With administration of glycyrrhizin 4 Gm daily it was possible to reduce the dose of cortisone gradually No appreciable variation was noted until the daily dose of cortisone had been reduced to 5 mg There was a slight decrease in serum sodium and chloride levels On the 24th day of the study

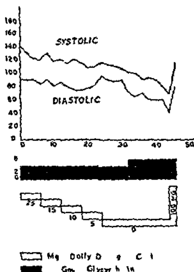


Fig 105—Do g d ff t f t d g y rrh n on blood p ur (C urt y f H dson P B r l New E gl d J M d 251 641 646 O t 14 1954)

cortisone was completely discontinued The systolic blood pressure became noticeably lower (Fig 105) The serum sodium level fell slowly (Fig 106) and urinary output slowly declined On the 34th day the patient became drowsy and lethargic These symptoms became progressively more severe for the remainder of the study The experiment was discontinued on the 45th day when a urinary tract infection developed and cortisone therapy was immediately reinstituted Six months later the patient died No residual adrenal tissue was found at autopsy

Glycyrrhizinic acid alone is inadequate to maintain patients after bilateral adrenalectomy However when it is

cortisone orally 1 or 2 mg daily inhibited the adrenal cortex in normal subjects and in women with the adreno genital syndrome Comparison of the effect of 25 mg doses of fluorohydrocortisone chlorohydrocortisone and hydrocortisone with that of cortisone in a man 63 with Addison s disease showed that results with hydrocortisone and cortisone were similar Chlorohydrocortisone and fluoro hydrocortisone however caused a marked fall in urinary so dium a rise in urinary potassium and glucose and eosino penia Fluorohydrocortisone produced the most pronounced change Sodium retention induced by fluorohydrocortisone persisted for a day after the drug was given Fluorohydro cortisone was also compared with aldosterone (electrocor tin) in a patient with Addison s disease (Fig 104) Each drug was given intravenously 200 µg in 250 cc of 5% dex trose in water during four hours and urinary sodium and potassium excretions were measured at intervals of two hours During infusion the effect of fluorohydrocortisone was similar to that of aldosterone but the effect of the for mer was more prolonged after the infusion was ended A man 37 admitted in severe addisonian crisis was treated with fluorohydrocortisone alone The ability to excrete a wa ter load returned to normal and he was maintained in ex cellent condition on 0 25 mg fluorohydrocortisone acetate orally each day Most patients maintained on fluorohydro cortisone received daily supplements of about 2 5 mg corti sone Little or no steroid material was found in the urine of any patient given fluorohydrocortisone The effect of 1 mg was equal to that of approximately 20 mg cortisone or hy drocortisone Patients on long term cortisone therapy could be transferred to fluorocortisone Thus adrenocortical func tion could be evaluated by standardized ACTH tests with out discontinuing effective therapy and jeopardizing the patient s health

Use of Glycyrrhizin after Bilateral Adrenalectomy Perry B Hudson Arnold Mittelman and Meir Podberezec[8] (New York) observed the effect of ammoniated glycyrrhizin after bilateral adrenalectomy on three patients with metastatic cancer One patient had a papillary carcinoma of the kid

(8) New England J Med. 251 641-646 Oct. 14 1954

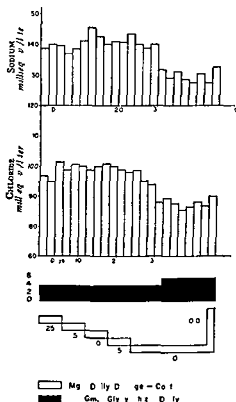
ome W Conn[9] (Univ of Michigan) describes the effects of an adrenal cortical tumor which was producing aldoster one in abnormally large amounts Aldosterone has been found to be a normal adrenal secretion and i present in abnormally high concentration in the urine of edematous nephrotics and in patients in cardiac failure or decompen sated hepatic cirrhosis All these patients have edema in contrast to absence of edema in the patient with primary aldosteronism

In the present case the striking abnormalities in the blood were hypokalemia hypernatremia and alkalosis Ur inary 17 ketosteroid and 17 hydroxysteroid excretions were normal Results of renal function studies were normal except for intermittent proteinuria and a low fixed specific gravity The concentrations of sodium and chloride in the sweat and saliva were greatly reduced and those of potas sium were abnormally high an inverse relationship to se rum concentrations ACTH accentuated these changes Ad ministration of potassium further lowered the sodium con centration in sweat and saliva The metabolic response to compound F and to ACTH was normal There was a mild increase in urinary nitrogen an increase in both 17 ketoster oids and 17 hydroxysteroids and a rise in fasting blood sugar Both compound F and ACTH increased potassium loss in the urine although the increased loss could be fully accounted for by the negative nitrogen balance After an initial retention there was diuresis of both sodium and chloride while compound F and ACTH were still being administered It appears that in the presence of excessive aldosterone activity an increase in 17 hydroxycorticoid levels acts as an antagonist to aldosterone with respect to the direction in which sodium ions move across cell mem branes In normal persons sodium and chloride diuresis occurred when 17 hydroxycorticoid levels were the lowest whereas in the patient with primary aldosteroni m diuresis was related to high levels

Clinically the patient had intermittent tetany pares thesias periodic severe muscle weakness and paralyses polyuria and polydipsia hypertension and no edema When the syndrome is fully developed there is an excessive

(9) J Lab & Cl M d 45 6 17 J y 1955

added to the maintenance regimen they can be maintained with amounts of cortisone which otherwise would have been inadequate In two cases cortisone was completely withdrawn for 10 days and 16 days without untoward



F g 106—Eff t f c t on d gly y h n on r m od m d chl de l l (C te y f H d P B r I N w E gla d J M d 251 641 646 O t 14 1954)

changes in metabolism or in the subjective sense of well being With the use of glycyrrhizin the development of symptoms of adrenocortical insufficiency is a gradual process extending over weeks

[Very similar observations in a patient with Addison s disease have been reported by Calvert (Lancet 1 805 Apr 17 1954) —Ed]

Primary Aldosteronism a New Clinical Syndrome Jer

ly since only about half of the patients with cortical hyper plasia have been reported to have had pituitary basophil adenomas Basophil adenomas have been observed in en docrinologically normal persons Demonstration of nodu lar hyperplasia of basophils after cortisone administration suggested that some of the basophil adenomas in Cush ing s syndrome were not true neoplasms but represented nodular hyperplasia secondary to hypercorticalism

Since normal hypothalamic histology was found in the presence of Cushing s syndrome with adrenal hyperplasia degenerative changes in the paraventricular nuclei cannot be the sole primary lesion in this condition Study of the pituitary in patients with Cushing s syndrome and in pa tients treated with cortisone revealed basophilic hyper plasia and hyalinized basophil cells in both groups The Crooke cells were therefore secondary to hyperadrenalcor ticalism and could not be considered primary in the patho genesis of Cushing s syndrome

Cushing s Syndrome Produced by Pituitary Basophil Carcinoma with Hepatic Metastases is described by W H Sheldon A Golden and P K Bondy[2]

Negress 26 was hospitalized with recurrent severe generalized headaches scotomas nausea and vertigo Failing vision edema hy pertension obesity hirsutism and purple striae rapidly developed Chemical studies disclosed elevated blood sugar glycosuria mild azotemia hypokalemia and hypo hloremic alkalosis which responded to potassium citrate Roentgenograms revealed demineralization of vertebral bodies Skull films and an intravenous pyelogram were negative She died suddenly during induction of ether anesthesia for surgical exploration of adrenal glands

Autopsy showed a basophil carcinoma of the adenohypophysis with local extension and multiple metastases to the liver Uninvolved portion of the adenohypophysis showed Crooke cell changes Bilat eral adrenal and parathyroid hyperplasia osteoporosis and acute and subacute pancreatitis were also noted

It is suggested that Cushing s syndrome represents the effects of altered adenohypophysial adrenocortical balance The site of the primary disturbance in rare instances is in the adenohypophysis as noted in this patient although more frequently it can be localized in the adrenal cortex The initiating lesion in many patients cannot be deter mined by available methods

[This and the preceding report emphasize our ignorance concerning the mechanism of regulation of adrenal function in Cushing s syndrome (see

(2) Am. J Med 17 134 14 J ly 1954

amount of a sodium retaining corticoid in the urine severe hypokalemia hypernatremia and alkalosis There is a renal tubular defect in reabsorption of water which is probably secondary to chronic hypokalemia Cases of potassium loss nephritis probably represent a later stage of primary aldosteronism Recommended therapy is total adrenalectomy followed by substitution therapy In the present case operation revealed a 4 cm right adrenal cortical tumor which was removed

[*A follow up report* (*J* Lab & Clin Med 45 661-664 April 1955) showed the tumor to contain 75 100 *times as much* aldosterone like material as is found in normal beef adrenal tissue The contralateral adrenal was normal except for a *narrowed zone fasciculata* Muscle biopsies showed increased intracellular sodium and decreased potassium. A renal tubular lesion consistent with chronic hypokalemic change was also seen in a biopsy specimen Postoperatively there were acute sodium diuresis and positive potassium balance hypernatremia hypokalemia and alkalosis disappeared within one to two weeks *Proteinuria and polydipsia* disappeared and the blood *pressure returned to normal levels* Muscle weakness tetany and slowing of mental processes all disappeared. Since the first report four additional cases with adenoma of the adrenal have been described In one other case *no adenoma could be found*—Ed]

Adenohypophysis and Hypothalamus in Hyperadrenal corticalism Lawrence W O Neal and Peter Heinbecker[1] (Washington Univ) studied the histology of the pituitary gland and of the hypothalamus in Cushing s syndrome and after cortisone administration *Differential cell counts* of the pituitary gland were made In one case of adrenal cortical carcinoma the pituitary gland contained 39% basophils and of these 67% were Crooke s cells In a case of adrenal cortical hyperplasia there were 3% *basophils all Crooke s cells in the pituitary* gland In nine patients who had received cortisone therapy the average percentage of basophils was 21 3 in two of these 1% and in one 3% of the basophils were Crooke s cells and in two others the Crooke cell count was 49 and 90% respectively In three control patients the average basophil count in the pituitary gland was 11 6%

It was considered possible that the hyalinized basophil cell might be easily reverted to the unhyalinized basophil cell The fact that the commonest single pituitary adrenal combination in Cushing s syndrome is basophil adenoma and cortical hyperplasia does not implicate basophil adenoma in the pathogenesis of Cushing s syndrome particular

(1) Ann Surg 141 1 9 Jan 1955

(Guy's Hosp London) Twenty one patients were treated by irradiation of the pituitary gland or by subtotal adrenalectomy Of 17 who received deep radiotherapy in doses of 3 800 r over four weeks 5 were also operated on Of the other 12 4 women improved whereas 8 patients including 6 men did not benefit from the treatment 7 of them now being dead Since this form of therapy yielded poor results surgical intervention was attempted

Perirenal air insufflation studies were performed a day before intravenous pyelography If the outline of the adrenal gland on one side remained obscure operation was first performed on that side to detect whether failure of delineation was due to a tumor or to atrophy resulting from a tumor in the other gland If the gland appeared normal or hyperplastic it was considered that the other was in a similar condition If air insufflation studies were noncontributory nine tenths of the gland on the left side was removed followed by total extirpation of the opposite one Cortisone was administered during the pre and post operative periods in the second stage of the operation and intravenous infusions containing 4% glucose in saline during the procedure

Subtotal adrenalectomy was done on 6 patients The only male patient in the group died two months after operation as an indirect result of hypertension Three had been in remission for 2½ year 1½ years and 7 months at the time of the report The other two neither of whom had undergone irradiation of the pituitary gland remained in remission for 1¾ years and 1 year and then began to relapse with signs of clinical deterioration increased urinary excretion of 17 ketosteroids and diminution of the number of circulating eosinophils They underwent a third operation at which the remaining portion of adrenocortical tissue was found to be hypertrophied

In a minority of cases unilateral adrenalectomy alone or combined with radiotherapy may prove sufficient In more rapidly progressive cases subtotal removal of adrenocortical tissue is required The pituitary gland should be irradiated after the first stage of adrenalectomy to prevent regeneration of the remaining portion of the adrenal gland

also McCann and Sydnor this YEAR BOOK p 605) The situation is comparable to that in hyperthyroidism An analogous confusion also has arisen as to the best method of treatment of adrenal hyperfunction The following series of articles present a variety of viewpoints—Ed]

Radiotherapy of Cushing s Syndrome is discussed by J F P Skrimshire[3] (London) Advantages of pituitary irradiation are its simplicity lack of operative risk and avoidance of chronic adrenal insufficiency If adrenal tumor can be excluded as the cause of the syndrome irradiation should be used initially Surgery may still be undertaken with undiminished chances of success *if the condition is not arrested or improved in 6 12 months*

Six women aged 19 36 with classic symptoms and laboratory signs of Cushing s syndrome received x ray therapy to the pituitary gland with a high voltage unit (250 kvp half value layer 1 75 mm Cu) Six circular beams of x rays at 50 cm focus skin distance were directed at the pituitary fossa with the aid of a plaster shell through portals arranged around the hairline A maximal dose of 4 000 5 000 r was given *in 28 30 days resulting in a skin dose of about 3 000 r* Larger doses were considered inadvisable because of possible late cerebral cortical atrophy Reducing diets were used to control obesity when necessary

Treatment led to slow but continued *improvement* Diminishing plethora and fading of skin striae usually became *evident in one to three months* Polycythemia present in two patients disappeared Hirsuties was not significantly affected and remained prominent in two Menses were re established in all patients but *remained irregular in two* and ceased again in one Glucose tolerance curves returned to normal Excretion of corticosteroids was reduced in four patients 17 Ketosteroid excretion moderately elevated in five was significantly reduced *in only two* Blood pressure fell but to normal levels in only two

Pituitary irradiation was considered preferable to surgery as the initial treatment of adrenal cortical hyperplasia An existence with controlled Cushing s syndrome is preferred to one with controlled adrenal insufficiency

Treatment of Cushing s Syndrome is described by P M F Bishop F N Glover R R DeMowbray and M G Thorne[4]

(3) Lancet 1 2 0 7 Feb 5 1955
(4) Ibid 2 1137 1140 Dec 4 1954

ment followed adequate hormone therapy usually within 12 hours

Early results in five of the six cases were gratifying Many of the signs and symptoms associated with Cushing s syndrome disappeared In the sixth patient who underwent adrenalectomy chiefly for relief of malignant hypertension neither blood pressure nor retinopathy was altered significantly three weeks after operation despite biochemical evidence of adequate surgery

Total Bilateral Adrenalectomy for Adrenal Cortical Hyperfunction William E Abbott William McK Jeffries Stanley Levey and Harvey Krieger[6] (Univ Hosp Cleveland) report results of total bilateral adrenalectomy in a patient with severe Cushing s syndrome followed for 23 months postoperatively

Woman 38 hospitalized with complaints of obesity and hirsutism had had hypertension for 5 year diabetes mellitus treated with insulin for 6 months mental disturbances requiring repeated hospitalizations for the previous 10 years infrequent menstrual periods for 20 years and amenorrhea for 10 months Exploratory laparotomy at age 25 was negative On admission she was lethargic and depressed and had pronounced facial hirsutism dry skin facial acne sparse cephalic hair trunk distribution of fat buffalo hump and purplish abdominal striae Blood pressure was elevated An x ray showed minimal osteoporosis The glucose tolerance curve was of diabetic type *17 ketosteroid excretion was increased and gonadotropin* excretion decreased After therapy with methyltestosterone for three weeks and cortisone the day before and the day of operation one stage bilateral adrenalectomy was performed Combined weight of the glands was 30 5 Gm Microscopic examination revealed diffuse and nodular hyperplasia of the cortex. Postoperatively she was given cortisone intramuscularly for three days then orally and on discharge was maintained on 25 mg orally twice daily Later a *small* cyst in the breast was removed Cortisone dosage was increased to 100 mg intramuscularly on the day of operation and subsequently she was maintained well on 37 5 mg daily Small amounts of desoxycorticosterone acetate were given because of low serum sodium level The menses became normal and hirsutism acne and the buffalo hump practically disappeared Blood sugar levels were normal Blood pressure stabilized at normal levels and she weighed 130 lb There was striking improvement in the mental state with absence of hallucinations depression and paranoid ideas

Total adrenalectomy was performed because of the severity and long duration of the disease and the accompanying psychosis The importance of regular maintenance dos

(6) J A M A 156 1168 1171 N 20 1954

Cushing's Syndrome Six Cases Treated Surgically were described by R N Beck D A D Montgomery and R B Welbourn[5] (Queen's Univ Belfast) Four of the patients were women Roughly 90% of one gland was removed followed by total extirpation of the other The operation was carried out in two stages separated by two or three weeks Apart from slight enlargement in some cases all the adrenal glands appeared normal No special precautions were taken with the operation on the first side In the second stage cortisone was given preoperatively and postoperatively in diminishing dosage and DCA postoperatively In three cases the adrenal remnant was encouraged to develop adequate function by stimulation with corticotropin Two types of adrenal insufficiency were noted after surgery

1 Acute peripheral circulatory collapse occurred in one case a day after operation it did not respond to cortisone and DCA and was treated successfully with nor epinephrine intravenously Lesser degrees of hypotension occurred on two occasions as a manifestation of the cortisone withdrawal syndrome but were controlled with DCA and cortisone

2 Cortisone withdrawal syndrome was noted in four patients postoperatively the time of onset being related to premature termination of hormone supplements Early morning nausea was the initial manifestation At first precipitated by ambulation and eased by rest it soon became persistent and was associated with intractable vomiting if allowed to progress unchecked followed by weakness irregular low grade pyrexia and tachycardia Moderate hypotension occurred in two cases Among early signs was a skin reaction involving the face and front of the neck and spreading in two cases to the outer aspect of the arms and back of the hands Erythema and pruritus developed skin was unusually dry and superficial exfoliation took place with casting of fine scales The appearance of the skin disorder at an early stage of the syndrome suggested its relationship to cortisone deficiency Improve

(5) Lancet 2 1140 1144 Dec 4 1954

appeared which receded in 24 hours She made a rapid recovery and was discharged on a maintenance dose of 37 5 mg cortisone acetate daily

Serum withdrawn from the patient 72 hours 6 months and 16 months after the anaphylactic reaction was injected intracutaneously into two normal subjects and ACTH put into the same site 24 hours later Positive reactions were obtained with two pork and one sheep preparation of ACTH After it was heated to 56 C for 30 minutes the patient s serum did not produce a positive skin reaction in passive transfer tests

Pregnancy and Adrenocortical Function Endocrine Studies of Pregnancy Occurring in Two Adrenal Deficient Women who showed evidence of gross adrenal insufficiency during their pregnancies are reported by A Gorman Hills Eleanor H Venning F Curtis Dohan George D Webster Jr and Edwin M Richardson [8] Both had had bilateral adrenalectomy for hypertension

Adrenal deficient women excrete increased amounts of 17 ketosteroids and neutral reducing lipids during pregnancy However since the Zimmermann and phosphomolybdate reactions are not specific and several endocrine organs increase and diversify their function during pregnancy it is possible that hormones other than adrenal steroids might be precursors of urinary compounds giving these reactions The increased excretion observable in the beginning of the second trimester progresses to term The increase in glycogenic corticoids in the urine in these patients was convincing evidence of increased endogenous production of compounds physiologically resembling cortisone under these conditions Corticotropin intravenously produced no significant increase of adrenal like steroids however No decrease in hormone requirement was noted in the one patient who regularly required maintenance therapy because symptoms of insufficiency appeared whenever the daily dose of 25 mg cortisone was reduced Thus pregnancy did not protect either patient against acute cortical insufficiency Complications of pregnancy and the stress of labor will usually call for additional replacement therapy as will stress in the nonpregnant adrenal deficient person

[The methods for measuring adrenal funct on are still too nonspecific to be entirely reliable in a situation as complicated as pregnancy Not until steroid excretory studies are reported in terms of spec fic identified

(8) J Cl I t 33 1466 1490 N mb 1954

age with cortisone the serious hazard of omitting even one dose and the necessity for increased dosage in times of stress in patients who have undergone total adrenalectomy cannot be overemphasized

[Although irradiation of the pituitary and hypothalamus does not always cause improvement it should probably be tried before surgery unless an adrenal tumor is suspected The evaluation of therapeutic results is complicated by the fact that like hyperthyroidism hyperadrenalism sometimes improves spontaneously The difficulties of handling adrenalectomized patients should not be minimized the authors discuss this problem and the following report describes a difficulty which would probably be encountered only in patients whose adrenals are unable to respond to ACTH —Ed]

Complications in Management of Cushing s Syndrome Including Anaphylactic Reaction to Intravenous Adrenocorticotropin after Subtotal Adrenalectomy were described by Gerald T Perkoff B V Jager and Frank H Tyler[7] (Univ of Utah)

Woman 40 had a history of amenorrhea hypertension progressive obesity weakness headaches and epistaxes She had truncal obesity moderate hirsutism atophic skin ankle edema and a blood pressure of 290/180 Laboratory study revealed an abnormal glucose tolerance curve increased excretion of 17 ketosteroid elevated plasma 17 hydroxysteroids and left ventricular enlargement In three operations 90% of the left adrenal an ovarian cystadenoma and the right adrenal were removed After the third operation a severe adrenal crisis occurred characterized by tachycardia severe hypotension nausea cold extremities diaphoreses and a feeling of impending doom

She was given large amounts of cortisone acetate aqueous adrenal extract and fluids parenterally with rapid improvement Bronchopneumonia developed but cleared with antibiotics Cortisone dosage was gradually reduced Signs of frank adrenal insufficiency recurred but were again controlled with increased cortisone and adrenal extract An episode of severe pyelonephritis precipitated another period of acute adrenal insufficiency A course of ACTH therapy induced a rise in plasma 17 hydroxycorticosteroids indicating the presence of residual functioning adrenal tissue Five months later 100 units of long acting ACTH intramuscularly had no effect on 17 hydroxycorticosteroids or 17 ketosteroid excretion After another five month interval an intravenous infusion of 25 units ACTH in 1 000 ml of 5% dextrose in water was begun in an attempt to stimulate the left adrenal remnant After receiving 50 ml of the solution the patient complained of a feeling of oppression became nauseated and vomited Severe facial and lingual edema developed blood pressure declined precipitously and the pulse rose Marked diaphoresis was followed by a cramping abdominal pain and a mucoid watery stool The infusion was immediately discontinued Generalized urticaria

(7) J Clin Endoc ol 15 36 37 M h 1955

the gastric washings were negative He continued taking 37 5 mg cortisone daily 6 Gm sodium chloride daily streptomycin and PAS and remained well

CASE 5—Man 51 with active pulmonary tuberculosis and Addison s disease collapsed after cholecystectomy He responded to adrenal cortical extract cortisone and fluids and was maintained on 50 mg cortisone and NaCl 6 Gm daily 1 Gm streptomycin weekly and 12 Gm PAS daily Within 25 days the tuberculous lesions were clearing There were two unexplained episodes of pyrexia with pleural and pericardial effusions Streptomycin and PAS were discontinued after a year and cortisone reduced to 12 5 mg daily for maintenance since the symptoms of Addison s di ease recurred on smaller doses He remained well and was working

Use of cortisone in physiologic dosage may account for its beneficial effect on existing tuberculosis The primary concern should be adequate treatment of Addison s disease in order to control the tuberculosis

Addison s Disease Associated with Thyroid Insufficiency and Atrophy (Schmidt Syndrome) J M B Bloodworth Jr Walter M Kirkendall and T Lyle Carr[1] (State Univ of Iowa) studied 24 hospital records and report clinical studies on 11 other cases of Addison s disease Adrenal insufficiency had usually prevailed for some time before onset of signs or symptoms of hypothyroidism The presence of pituitary insufficiency was ruled out by clinical evaluation and autopsy findings Of 12 autopsies 4 disclosed absence or almost complete destruction of thyroid gland

The most consistent finding in the series was extensive lymphocytic infiltration with follicle formation and fibrosis In these circumstances absence of adrenocortical hormones may conceivably cause hypertrophy of lymphoid tissue with secondary destruction of the thyroid acini In 9 of the 35 patients clinical hypothyroidism was present others had symptoms that could be attributed to hypothyroidism and 7 showed laboratory evidence of hypothyroidism In two patients with clinical evidence of myxedema tests showed normal thyroid function but four whose tests showed abnormal thyroid function had no clinical evidence of hypothyroidism Thus in 13 patients there was either clinical or laboratory evidence of hypothyroidism and almost all had some evidence of thyroid abnormality

In view of the widespread and multiple actions of ad

(1) J Clin E doc 1 14 540 553 M y 1954

compounds rather than such heterogeneous collections as 17 hydroxy corticosteroids and glycogenic steroids will apparent contradictions such as are described here be resolved —Ed]

Treatment of Coexisting Addison s Disease and Active Pulmonary Tuberculosis with streptomycin PAS isonicotinic acid and supplementary cortisone acetate and sodium chloride was carried out in five patients by J S L Browne M Aronovitch J C Beck W Leith and J F Meakins[9] (McGill Univ) Improvement was prompt with disappearance of acid fast bacilli and had been maintained for 1 3½ years after active antituberculous therapy was stopped Cortisone acetate and sodium chloride were continued Four of the five patients were carrying on full time occupations Spread of pulmonary tuberculosis on replacement doses of cortisone acetate had not occurred

CASE 1 —Woman 43 with a five year history of Addison s disease was admitted for treatment with cortisone Chest x ray revealed tuberculosis Cortisone acetate 50 mg daily was begun and two weeks later *when acid fast bacilli were cultured from gastric washings* streptomycin 1 Gm daily and PAS 6 8 Gm daily were started Within two months definite clearing of the infiltration was demonstrated After three months of cortisone therapy menses and hypertension returned After eight months the tuberculosis was considered arrested and streptomycin was stopped She was maintained on 37 5 mg cortisone acetate 6 Gm sodium chloride and 8 15 Gm PAS daily On follow up she was working in good health and without active pulmonary tuberculosis

CASE 2 —Man 48 developed Addison s disease while in a sanatorium for active pulmonary tuberculosis With cortisone sodium chloride streptomycin and PAS there were rapid clearing of the lesions on x ray disappearance of cough and sputum and progressive weight gain *After seven months sputum and gastric washings were* negative on culture He was discharged and remained well

CASE 3 —Man 56 with Addison s disease and active pulmonary and epididymal tuberculosis was treated with DCA NaCl and PAS Sputum cultures became negative but after a year of therapy active tuberculosis developed in another lobe Cortisone streptomycin and PAS were administered with improvement in Addison s disease within three weeks After a year the tuberculosis was considered arrested and streptomycin and PAS were stopped He was maintained on 37 5 mg cortisone and then on 25 mg daily

CASE 4 —Man 32 with known tuberculosis for eight years developed Addison s disease He was treated with cortisone acetate and DCA with dramatic improvement Sputum was positive for acid fast bacilli *but he refused treatment for his tuberculosis* Eventually he was placed on streptomycin and PAS therapy and soon

(9) Am J M S 2 8 491 505 N mbe 1954

before during and after ACTH and cortisone therapy con vinced Henriette Loewenberg Wayne[3] (V A Hosp Bronx N Y) that the stability of the electrical activity of the cortex before hormone therapy is important in evaluating results of treatment on the EEG Patients with initially normal or borderline EEG records showed relatively few or no changes during hormone therapy However those with moderate or grossly pathologic brain wave patterns usually manifested an increase in the defect and occasionally the development of patterns compatible with those seen in convulsive disorders

Four patients had clinical seizures during or shortly after ACTH or cortisone therapy Three had collagen disease and more or less grossly abnormal EEG s before hormone therapy exemplified by slowing of activity and mild paroxysmal features Two of these had lupus erythematosus autopsy on one showed no cerebral abnormalities and the other no clinical evidence of central nervous system involvement before status epilepticus occurred Two of the four patients with seizures and psychotic features showed signs and symptoms of potassium deficiency Despite a reported decrease in incidence of psychosis when ACTH dosage was reduced potassium salts were added and sodium intake was restricted Wayne concurs with the view that the effects of potassium depletion on the central nervous system activity indicate only one phase of more complex processes which take place when such complications as EEG *changes convulsions and psychotic* manifestations occur The overt symptomatology of a psychosis may be determined somewhat by the patient s basic personality structure as well as by his reaction to metabolic and emotional stresses accompanying illness and the changes produced by therapy

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THE PITUITARY GLAND

Mechanism of Endocrine Control of Melanin Pigmentation Aaron Bunsen Lerner Kazuo Shizume and Irby Bun

(3) J Cl E doc 1 14 1039 1045 S pt mb 1954

renocortical hormones it is probable that adequate circulating cortical hormones are necessary for normal thyroid activity Reduction in adrenocortical function may reduce thyroxin output and alter its peripheral activity

True Pituitary Addison s Disease—Pituitary Unitropic Deficiency (15 Year Follow up) is reported by Arthur Steinberg F R Shechter and H I Segal (Philadelphia)

Woman 50 was hospitalized six times in 15 years with weakness numbness fatigability weight loss anorexia nausea vomiting intermittent diarrhea dizziness syncope depression skin pigmentation and hypoglycemia due to stress Blood pressure varied from 80/60 to 118/70 She was poorly nourished Deep pigmentation increased in the infraorbital region in areas of tight clothing flexor areas the hard and soft palate and buccal mucosa She had inguinal adenopathy emphysema a small heart hepatomegaly cervical lordosis and tenderness over a cervical vertebra Laboratory studies revealed normal BMR hemogram blood sugar and serum sodium blood urea nitrogen and serum potassium levels urinary gonadotropin and estrogen values and consistently low 17 ketosteroid excretion When given a high calorie protein and carbohydrate diet and 40 units of ACTH gel intramuscularly twice weekly and vitamins she improved subjectively appetite increased and she gained weight Nausea, vomiting anorexia and diarrhea subsided she became more alert and pigmentation decreased markedly

Differential diagnosis included primary Addison s disease Addison s disease secondary to corticotropin deficiency (true pituitary Addison s disease) anorexia nervosa and Simmonds disease The signs and symptoms indicated Addison s disease and diagnosis was confirmed by low 17 ketosteroid excretion decreased body sodium and chloride and elevated potassium levels flat glucose tolerance curve and small heart After ACTH therapy the eosinophil count decreased urinary 17 ketosteroids increased and she improved significantly which would not have occurred in primary Addison s disease The normal urinary gonadotropin and estrogen level and normal thyroid function eliminated Simmond disease and diagnosis of true pituitary Addison s disease was made

Convulsive Seizures Complicating Cortisone and ACTH Therapy Clinical and Electroencephalographic Observations In 43 nonepileptic patients without obvious metabolic endocrine or emotional disorders serial E E G s made

(2) J Clin E doc 1 14 1519 15 9 December 1954

cytes (Fig 107). Other steroids such as progesterone may also be important In patients with adrenocortical insufficiency the following sequence is postulated decreased adrenocortical function results in decreased hydrocortisone production provoking a compensatory increase in pituitary activity and increased secretion of MSH and ACTH The function of MSH would no longer be inhibited peripheral

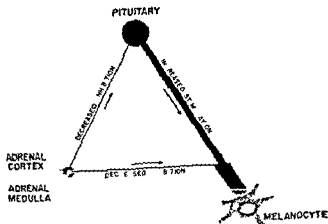


Fig 108 —Addison ... MSH ... hydrocortisone ... of ... of the pituitary ... MSH by ... (C ... A B ... J Cl Endoc ... 14 1463 1490 December 1954)

ly if adrenaline were lacking because of a destroyed adrenal medulla (Fig 108)

Cortisone and hydrocortisone can prevent hyperpigmentation in patients with bilateral adrenalectomy or Addison s disease and can diminish pigmentation already present in Addison s disease The action of adrenaline and nor adrenaline although potent in vitro has not proved to be of clinical significance The pigmentation associated with ACTH administration is probably due to contamination with MSH which apparently is a distinct pituitary hormone

Determination of Melanocyte Stimulating Hormone in Urine and Blood was made by Kazuo Shizume and Aaron

ding[4] (Univ of Oregon) report that an anterior pituitary fraction containing a high concentration of melanocyte stimulating hormone (MSH) caused darkening of the skin *and nevi and formation of new nevi* in seven subjects including one patient with hypopituitarism and one with bilateral adrenalectomy Up to 200 mg MSH was injected daily intramuscularly about 10 million times the amount required to darken frog skin No significant changes in

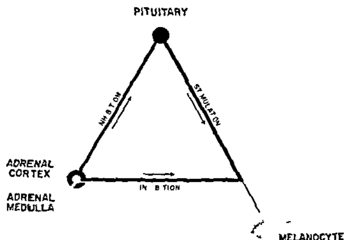


Fig 107—N m l p gm t t n Hydrocort on h b t tp t of MSH by th p t t ry gl d Nor d l d ad l e h b t MSH a t on on p gm t form g cell (Courtesy of Le e A B et l J Cl n End cri ol 14 1463 1490 Decemb r 1954)

circulating eosinophils or urinary 17 ketosteroid excretion were observed There was no change in the blood glucose or serum copper levels Only 1 4% of the injected MSH was excreted in the urine indicating either rapid destruction or binding by the tissues

Normally several hormones control pigmentation MSH from the pituitary *gland increases pigmentation* Hydrocortisone from the adrenal cortex probably inhibits the release of MSH Adrenaline and nor adrenaline from the adrenal medulla and adrenergic nerve endings probably can reduce or prevent the action of MSH on the melano

(4) J Cl E doc ol 14 1463 1490 Dec mbe 1954

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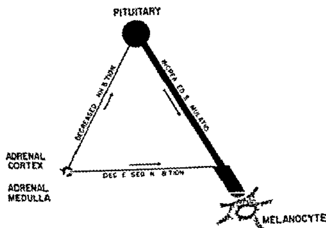


Fig 108—Add n d e MSH utp t becau hyd ocort son hbtion f th pt t ry s d ed If the d en l m d lla d t y d inhibit f MSH b d enal e a d no d l em d (Court y f Le A B et l J Cl E docri l 14 1463 1490 December 1954)

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Bunsen Lerner[5] (Univ of Oregon) with quantitative assay procedures Using isolated frog skin they found that blood melanocyte stimulating hormone (MSH) concentration increased with increase in urinary excretion of MSH The tests appeared specific for MSH Adrenaline noradrenaline hydroxytyramine serotonin ergotamine derivatives and mesantoin® ordinarily affect frog melanocytes but

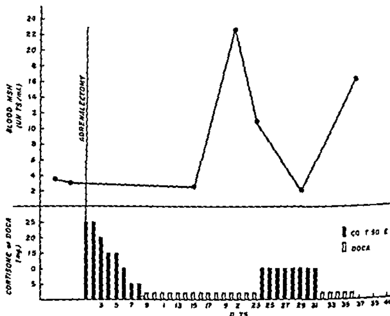


Fig 109—Blood MSH c e tr t o cr as d in dog afte a] enalectomy but et rned to m l ft r dm t t on f c rt one (C t y f Sh m k and Lerner \ B J C n Endoc inol 14 1491 1510 December 1954)

did not interfere with the assays because they were not extracted with MSH

The concentration of MSH in urine and blood was the same for normal males and females The 24 hour urinary excretion values ranged from 7 5 to 47 5 units average 27 7 In blood the range of MSH was from 0 4 to 2 2 units/ml average 1 3

During pregnancy MSH excretion was elevated at the end of the second month and continued to increase until term Following delivery there was rapid return to normal

(5) J Clin Endocrin L 14 1491 1510 December 1954

in a few days Increased quantities of MSH were excreted by 7 of 12 patients with Addison's disease and by 4 of 8 with bilateral adrenalectomies Some of them excreted normal amounts of MSH probably because they were receiving cortisone In single patients with new lentigines alopecia areata totalis or retinitis pigmentosa MSH was also elevated Negroes albinos and those with vitiligo had normal MSH excretion values Two of eight patients with decreased pituitary function excreted decreased amounts of MSH

Administration of cortisone to a patient with high levels of MSH in the blood and urine reduced the hormone concentration to normal Following adrenalectomy the blood MSH level increased markedly in a dog but returned to normal after cortisone was administered (Fig 109)

[These studies clarify the mechanism of the pigment changes in adrenal and pituitary insufficiency and the role of intermedin in these changes —Ed]

Acromegaly J M Finlay and R Ian Macdonald[6] (Toronto) reviewed the clinical radiologic and endocrinologic features in 12 patients with acromegaly None had a family history of acromegaly and only three were 6 ft tall and over Initial symptoms included enlargement of the face hands and feet in 11 patients headache fatigue and weakness and loss of libido in 7 each arthralgia in 6 back pain in 5 and blurring of vision amenorrhea increased sweating and attacks of dizziness in 1 each All patients had enlargement of the jaw 10 had enlargement of the hands and feet 6 macroglossia 5 kyphosis 5 visual defects 4 hypertension 2 hepatomegaly 2 muscle impairment 2 epilepsy and 1 each a sensory lesion ataxia splenomegaly and cardiomegaly Five patients had abnormal glucose tolerance curves four elevated BMR s and one each elevated fasting blood sugar elevated serum phosphorus and increased excretion of urinary 17 ketosteroids

Radiologic changes included a generalized overgrowth of bones cortical thickening with circumferential increase and coarsening of structure The sella was larger than normal in nine patients normal in two and smaller than normal in one The frontal sinuses were commonly enlarged Prominence of the symphysis menti was more com

(6) F A J 71 345 353 O t le 1954

mon than enlargement of the inferior dental arch Widening of the vertebral bodies present in six patients was due to anterior and lateral accretions of new bone Tufting of the distal phalanges with cortical thickening was frequently present

It was concluded that visual field defects are not common early signs of acromegaly Radiologic changes and changes in the face and body are usually of greater importance in early diagnosis The size of the sella turcica bears no relation to the presence of visual field defects

Effect of Growth Hormone on Muscle Potassium and on Extracellular Fluid Adrienne A Batts, Leslie L Bennett Joseph Garcia and Jerome Stein[7] (Univ of California) measured the body thiocyanate space plasma volume and muscle sodium and potassium in normal and hypophysectomized rats and in hypophysectomized rats given 1 mg growth hormone daily In seven series of 13 22 animals each hypophysectomy produced no change in the thiocyanate space which was 34 2% of body weight and in normal rats was 33 2% One mg of growth hormone daily for 2 10 days elevated thiocyanate space to values as high as 42 5% of body weight In four series of 8 19 animals each 1 mg growth hormone daily increased the plasma volume by 0 3 0 5% of body weight Sodium and potassium plasma levels remained unchanged

Potassium concentration in the muscle was lowered significantly following hypophysectomy in 10 of 11 groups of animals average value being 98 6 mEq /kg as against 104 7 mEq /kg in normal control One mg of growth hormone daily for at least 10 days restored the muscle potassium concentration toward normal Concentrations of sodium and nitrogen in the muscle remained unchanged

To determine whether these effects were specific for growth hormone similar experiments were carried out with ACTH pitressin® thyroxin and testosterone propionate None produced the effects observed with growth hormone Gonadectomy did not alter the response to growth hormone Restriction of food intake of normal animals did not cause reduction of muscle potassium concentration It is therefore concluded that growth hormone causes an ex

(7) Endocrinology 55 456-463 October 1954

pansion of the extracellular fluid space explaining the previously observed sodium and chloride retention The hormone has some role in maintaining the muscle potassium level

Body Water and Sodium in Patients with Acromegaly were measured by Denis Ikkos Rolf Luft and Bjorn Sjogren[8] (Serafimer Hosp Stockholm) In 18 patients average total body water was 55 8% of body weight or 23 2 L/sq m of body surface (normal in nine healthy subjects 49 7% and 18 6 L) constituting statistically significant differences The amount of total exchangeable sodium in the acromegalics was 52 8 mEq/kg body weight or 2174 mEq/ q m of surface area or 94 3 mEq/L of total body water These figures were significantly higher than corresponding figures in the healthy subjects

The extracellular water also was significantly increased in acromegalics whether the calculations were made from the inulin or thiosulfate spaces The amount of intracellular water expressed as per cent of body weight was of the same magnitude in both groups Expressed as L/sq m of surface area it was different (higher) in the acromegalics only when calculated from the inulin space When expressed as per cent of total body water it was significantly higher in the acromegalics only when calculated from the thiosulfate space

The distribution of exchangeable sodium between the intra and extracellular fluid compartments in the acromegalics did not differ from that in the healthy subjects but the apparent mean intracellular sodium concentration was significantly higher

[The demonstration that fluid and electrolyte changes in acromegalic patients are like those produced by growth hormone in rats offers additional evidence that acromegaly is chiefly a result of excessive growth hormone production The expanded extracellular fluid volume may account for the tendency of acromegalic patients to develop congestive failure late in the course of their disease.—Ed]

Incidence of Postpartum Hypopituitarism H L Sheehan[9] (Univ of Liverpool) reviews the pathogenesis of postpartum hypopituitarism and presents clinical histories and autopsy findings on nine cases Severe blood loss or shock at delivery is the initiating factor retained placenta or postpartum hemorrhage being the commonest cause

(8) J Ch I t 33 989 994 J ly 1954
(9) Am J Ob t & Gy ec 68 20 2 3 J l 1954

The blood supply to the anterior lobe of the pituitary is interrupted and infarction results. In about half the cases 95-98% of the anterior lobe is necrosed; only the pars tuberalis and a few patches of subcapsular parenchyma are spared. The necrosed area heals to a small fibrous scar which remains unchanged. If more than two thirds of the anterior lobe is infarcted, some pituitary insufficiency results. If practically all of the lobe is involved, insufficiency is severe.

Follow-up on a series of obstetric patients with hemorrhage or shock at delivery showed that about 15% of the survivors of moderate obstetric hemorrhage or shock and 40% of the survivors of severe hemorrhage or shock had

INCIDENCE OF SYMPTOMS OF HYPOPITUITARISM IN LIVE PATIENTS SOME YEARS AFTER DELIVERY

Hemorrhage and/or Shock at Delivery	Subsequent Clinical Hypopituitarism		
	None	Partial	Severe
None or trivial	90	0	0
Moderate	52	7	2
Severe or very severe	24	11	6

subsequent hypopituitarism (table). It was calculated that about 8% of patients with moderate hemorrhage at delivery and about 53% with severe or very severe hemorrhage should, if they continued to live for months or years later, have clinical evidence of hypopituitarism during that time.

Patients with pituitary necrosis may die during the puerperium of the same causes as do other obstetric patients. The lesion in the pituitary is not fatal at this stage. Autopsies on patients who died in the puerperium with or without pituitary necrosis always showed an adequate cause of death, such as puerperal sepsis or pulmonary embolism.

Postpartum hypopituitarism has been described frequently in England but continues to be rather a rarity in the American literature. Sheehan's description of the difficulty of following these lethargic deteriorated patients may explain why the diagnosis is sometimes missed. In the immediate postpartum period the patient appears normal. A month or so after delivery the severely ill woman becomes withdrawn, lies huddled in bed, neglecting her housework and personal hygiene. She becomes estranged from her husband and children and they therefore have little interest in her welfare. The undiscerning physician may consider her sluggish responses and negativistic attitude to be psychogenic. Before the diagnosis is recognized she may die in hypopitu[illegible] In view

of the high incidence of this complication of obstetric shock all patients whose deliveries have been complicated should be followed aggressively for at least a year to be certain that the syndrome is not developing —Ed]

Diagnosis and Treatment of Hypopituitarism in nine patients is described by S R F Whittaker and T P Whitehead[1] (Warwick Hosp) Of the seven women studied five had experienced severe postpartum hemorrhage In the other four subjects two of whom were men the etiologic process could not be ascertained Average duration of symptoms was over 10 years and the clinical picture varied The most constant features were fatigue mental inertia extreme sensitivity to cold loss of libido amenorrhea loss of pubic and axillary hair and a slow monotonous type of speech The typical facial characteristics were lack of animation waxy pallor slight puffiness of the skin and thinning of eyebrows and hair

Biochemical investigations revealed a high incidence of abnormality particularly in the basal metabolic rate urinary 17 ketosteroids insulin tolerance reaction and reaction to the Kepler water test Biochemical data in 51 cases

RESULTS OF PITUITARY FUNCTION TESTS

Test	Patients Tested	Abnormal Result
BMR (abnormal if less than −10% of normal)	54	48
17 ketosteroids (abnormal if less than 2 mg /day)	54	47
Insulin tolerance (interpretation Fraser and Smith 1941)	45	38

abstracted from the literature and in the present series are given in the table In each of the tests 85 90% of the patients had abnormal reactions

Excellent results were obtained in eight patients treated with cortisone One of them experienced an untoward reaction described in the following case report

Woman 56 with hypopituitarism for many years responded well to ACTH but relapsed completely 10 days after injections were discontinued. She was then given 50 mg cortisone daily and after three doses appeared to be responding On the fourth day she became listless and gradually sank into coma which continued for the next four days Injections of cortisone were continued daily Serum sodium and potassium levels were normal and blood sugar content 160 mg /100 ml During coma there was a fall in rectal temperature

(1) Brit M J 2 265 269 T 1 31 1954

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(1) Brit M J 2 65 269 J ly 31 1954

to 87 F Injections of cortisone were stopped and she responded well to warmth supplied by electric cradles

In addition to cortisone therapy administration of thyroid produced further improvement in all cases It was suggested that treatment should start with a daily dose of 25 mg cortisone and ½ gr thyroid and be regulated over a period of months by the clinical response In the two men, addition of methyltestosterone induced an increase in libido strength of erection and growth of pubic hair

Puerperal Panhypopituitarism Ian MacGillivray and J F Adams[2] (Univ of Glasgow) present a case in which signs and symptoms of Simmonds disease and diabetes insipidus developed simultaneously post partum

Woman, 29 para II hospitalized in collapse following a severe postpartum hemorrhage was treated with plasma whole blood and ergonovine Vaginal bleeding began and became excessive Uterine exploration revealed retained placental tissue The puerperium was complicated by fever and thrombosis of the superficial calf veins The uterus involuted at the normal rate but lactation was never established The breasts remained soft and painless No estrogens were given The urinary output was high for a few days Diabetes insipidus was considered as a possible cause of polyuria but since the urinary output was normal on subsequent days and the blood chloride level was 102.6 mEq /L the diuresis was considered due to loss of edema fluid An insulin sensitivity test was normal Excretion of 17 ketosteroids was below normal Simmonds disease was suspected but diagnosis could not be established Three months later the patient complained of polydipsia polyuria marked tiredness loss of libido hypersensitivity to cold amenorrhea weight gain and persistence of frontal headaches There was no axillary hair and pubic hair was scanty She now had a marked hypersensitivity to insulin with increased tolerance to glucose A diagnosis of Simmonds disease was made Marked polyuria and polydipsia hyperchloremia low urinary chlorides and low specific gravities of the urine pointed to diabetes insipidus Voluntary restriction of fluid intake did not raise the specific gravity appreciably Pitressin® tannate in oil intramuscularly produced a striking decrease in urinary output The diabetes insipidus was controlled with regular injections of pitressin® tannate She menstruated once after injections of anterior pituitary hormones On three occasions thereafter she menstruated spontaneously without further injections of hormones and the scalp hair was beginning to grow

The spontaneous tendency to recovery from Simmonds disease without any alteration in the degree of diabetes insipidus suggested the occurrence of individual lesions

(2) J Obst & Gynec Brit Emp 61 738 743 December

in the anterior and posterior lobes of the pituitary The area of the anterior lobe concerned with production of the diuretic factor presumably was not involved

The presence of profound shock is apparently essential to production of the combined lesions in the anterior and posterior lobes The low incidence of such cases is pre sumably due to death from profound shock too early for the lesions to develop

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Coma and Allied Disturbances of Consciousness in Hy popituitarism Disturbances of consciousness varying from hypersomnia mild confusion and impaired cerebration to stupor and profound coma were encountered in 17 pa tients with hypopituitarism by J E Caughey and Oliver Garrod[3] The numerous immediate precipitating factors included cerebral surgery pituitary apoplexy infections hypoglycemia drugs and anesthetics electrolyte disturb ances water intoxication and cerebral anoxia

Prolonged coma followed intracranial operations in four patients with pituitary tumors All had hypogonadism but in only two was there clear evidence of adrenal or thyroid failure All eventually recovered though they had complete amnesia for the period of coma So called pituitary apo plexy, a rare syndrome caused by hemorrhage into a pi tuitary adenoma was seen in one patient Infections such as colds influenza and gastroenteritis caused drowsiness confusion and eventually coma in eight patients One pa tient slept for 48 hours during influenza and other fevers and another slept for 2 days during an attack of influenza In a patient with Sheehan s syndrome features of an ad renal crisis developed during a febrile period During the next seven years she had many attacks of coma and stu por mostly precipitated by gastroenteritis or upper respira tory infections and all accompanied by fever Thyroid sub stance and testosterone implants were ineffective Since cortisone therapy was started 12 5 25 mg a day she has

(3) B t M J 2 554 560 Sept 4 1954

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[Postpartum pituitary necrosis usually spares the posterior pituitary This report would therefore be of great interest if the diagnosi of dia betes insipidus were securely established Unfortunately in the absence of an osmotic response test (uch as that of Hickey and Hare J Clin. Invest 23 768 775 1944) and with the data supplied by the author the possibility of psychogenic polydipsia still cannot be ruled out —Ed]

Coma and Allied Disturbances of Consciousness in Hypopituitarism Disturbances of consciousness varying from hypersomnia mild confusion and impaired cerebration to *stupor and profound coma were encountered in 17* patients with hypopituitarism by J E Caughey and Oliver Garrod[3] The numerous immediate precipitating factors included cerebral surgery pituitary apoplexy infections hypoglycemia drugs and anesthetics electrolyte disturbances water intoxication and cerebral anoxia

Prolonged coma followed intracranial operations in four patients with pituitary tumors All had hypogonadism but in only two was there clear evidence of adrenal or thyroid failure All eventually recovered though they had complete amnesia for the period of coma So called pituitary apoplexy, a rare syndrome caused by hemorrhage into a pituitary adenoma was seen in one patient Infections such as colds influenza and gastroenteritis caused drowsiness confusion and eventually coma in eight patients One patient slept for 48 hours during influenza and other fevers and another slept for 2 days during an attack of influenza In a patient with Sheehan s syndrome features of an adrenal crisis developed during a febrile period During the next seven years she had many attacks of coma and stupor mostly precipitated by gastroenteritis or upper respiratory infections and all accompanied by fever Thyroid substance and testosterone implants were ineffective Since cortisone therapy was started 12 5 25 mg a day she has

(3) B t M J 2 554 560 Sept 4 1954

to 87 F Injections of cortisone were stopped and she responded well to warmth supplied by electric cradles

In addition to cortisone therapy, administration of thyroid produced further improvement in all cases It was suggested that treatment should start with a daily dose of 25 mg cortisone and ½ gr thyroid and be regulated over a period of months by the clinical response In the two men addition of methyltestosterone induced an increase in libido strength of erection and growth of pubic hair

Puerperal Panhypopituitarism Ian MacGillivray and J F Adams[2] (Univ of Glasgow) present a case in which signs and symptoms of Simmonds disease and diabetes insipidus developed simultaneously post partum

Woman 29 para II hospitalized in collapse following a severe postpartum hemorrhage was treated with plasma whole blood and ergonovine Vaginal bleeding began and became excessive Uterine exploration revealed retained placental tissue The puerperium was complicated by fever and thrombosis of the superficial calf veins The uterus involuted at the normal rate but lactation was never established The breasts remained soft and painless No estrogens were given The urinary output was high for a few days Diabetes insipidus was considered as a possible cause of polyuria but since the urinary output was normal on subsequent days and the blood chloride level was 102.6 mEq /L the diuresis was considered due to loss of edema fluid An insulin sensitivity test was normal Excretion of 17 ketosteroids was below normal Simmonds disease was suspected but diagnosis could not be established Three months later the patient complained of polydipsia polyuria marked tiredness loss of libido hypersensitivity to cold amenorrhea weight gain and persistence of frontal headaches There was no axillary hair and pubic hair was scanty She now had a marked hypersensitivity to insulin with increased tolerance to glucose A diagnosis of Simmonds disease was made Marked polyuria and polydipsia hyperchloremia low urinary chlorides and low specific gravities of the urine pointed to diabetes insipidus Voluntary restriction of fluid intake did not raise the specific gravity appreciably Pitressin® tannate in oil intramuscularly produced a striking decrease in urinary output The diabetes insipidus was controlled with regular injections of pitressin® tannate She menstruated once after injections of anterior pituitary hormones On three occasions thereafter she menstruated spontaneously without further injections of hormones and the scalp hair was beginning to grow

The spontaneous tendency to recovery from Simmonds disease without any alteration in the degree of diabetes insipidus suggested the occurrence of individual lesions

(2) J Obst & Gynaec B t Emp 61 738 743 Dec mber 1954

sweating and nervousness relieved by food He was slightly obese Th skin was slightly yello ish dry and warm the hair dry and brittle Th thyroid was not palpable Blood pressure and pulse were normal as were genitalia and secondary sex characteristics Results of laboratory studies were normal except that thyroid deficiency was indicated by low BMR protein bound iodine and radioactive iodine uptake and high serum cholesterol level supported by absence of thyroid and thyrotropic activity in the serum Adrenocortical and gonadal functions and gonadotropic activity were normal

After 30 mg lyophilized beef thyrotropin intramuscularly daily for 3 days he showed clinical and laboratory improvement for 10 days Similar response followed administration of growth hormone contaminated with thyrotropin l thyroxin produced clinical and laboratory improvement but prompt relapse followed discontinuation After four months of l thyroxin therapy repeat assay of serum thyrotropin revealed high activity probably due to stimulation of the pituitary by l thyroxin in small doses

[The rise of serum TSH after l thyroxin treatment is confusing If the pitu tary were capable of producing TSH why was it not producing large amounts while the patient was hypothyroid Why should thyroxin which ordinarily suppres es TSH secretion cause a supernormal level in thi patient? All of the criteria usually considered necessary for the diagnosis of secondary hypothyroidism are included in this carefully studied case yet the peculiar response of the serum TSH throws doubt on the diagnosis One wonders whether the measurement of serum thyrotropin is sufficiently ac urate and specific to justify these doubts —Ed]

Starvation State and Functional Hypopituitarism William H Perloff Eunice M Lasche John H Nodine Norman G Schneeberg and Carol B Vieillard[5] (Philadelphia) attempt to assess the value of clinical and laboratory studies in differentiating hypopituitarism produced by severe malnutrition from that due to destruction of the anterior pituitary gland from various other causes such as postpartum hemorrhage or tumor Functional activity of the pituitary gland may be greatly impaired by starvation The first manifestation is commonly a decrease in activity of the gonads and thyroid adrenocortical activity being maintained for a longer period This type of functional hypopituitarism differs from organic hypopituitarism only in that it may be reversed by refeeding and recognizable structural changes in the anterior lobe of the pituitary are absent or slight compared to those in hypopituitary cachexia Lack of sustained and adequate response to specific endocrine therapy may offer evidence in a negative way Hypopituitary cachexia usually requires replacement therapy where

(5) J A M A 155 1307 1313 A g 7 1954

been free from coma for two years despite repeated infections. Hypoglycemia occurred spontaneously and also followed injection of insulin to which these patients are extraordinarily sensitive. Hypersensitivity to drugs and anesthesia was evident in patients with hypopituitarism. Sodium depletion sufficient to cause collapse seldom occurs spontaneously but losses during surgery, infections or gastroenteritis are not well tolerated and may have been a critical factor in precipitating coma. Patients with hypopituitarism cannot excrete a water load rapidly and are prone to water intoxication. Six patients at times had hypotensive postural faints apparently due to cerebral anoxia.

Regular cortisone therapy with increased dosage during intercurrent infections, surgery and other stresses *will protect the patient with hypopituitarism from hypersomnia and coma.* If there is clinical or laboratory evidence of hypothyroidism thyroid substance should also be given. If coma develops a precipitating infection should be sought and the appropriate antibiotic started. It is difficult to evaluate other therapy because of spontaneous recovery after correction of the precipitating factor. If the body temperature is very low the patient should be immersed in a warm bath. Blood sugar, plasma sodium, urea and bicarbonate levels and hematocrit should be determined quickly. Without waiting for the result hydrocortisone should be given intravenously, and glucose either intravenously or orally. Further therapy must be guided by clinical and biochemical findings. Small amounts of desoxycorticosterone acetate may be beneficial during the first few days.

Solitary (Monotropic) Thyrotropin Deficiency with Secondary Hypothyroidism. Observations on Response to Thyrotropin, Growth Hormone and Sodium l-Thyroxin. Martin C. Sampson, Edward Rose and Edward Herbert[4] (Univ. of Pennsylvania) report on a patient with anterior pituitary deficiency limited to thyrotropic hormone.

Man 27 had recurrent weakness, lassitude, drowsiness, cold intolerance, polyuria, polydipsia, polyphagia, chest pain, exertional dyspnea and headache. Several hours of fasting induced faintness

(4) Am. J. M. Sc. 17:871-8 9, December 1954

nals The decreased BMR is thought to be due to malnutrition

It is felt that in anorexia nervosa there is no primary insufficiency of the anterior pituitary but a regression of the whole endocrine system to childhood levels This corresponds with the psychic situation of the patients who seem to seek a return to childhood

[The low BMR in malnutrition is not necessarily a reflection of decreased thyroid function since many of these patients have normal PBI and I^{131} uptakes Consequently the only systems which are usually hypoactive are those concerned with ovarian function Calling this a regression to childhood levels is picturesque but oversimplified —Ed]

CARBOHYDRATE METABOLISM

Design of Insulin Trials Insulin Zinc Suspension (Lente) Ronald G Paley[7] (Univ of Leeds) compared the action of insulin zinc suspensions to that of mixtures of soluble and protamine zinc insulin in four patients with unstable diabetes

Observation of control periods on combined soluble and protamine zinc insulins six months apart revealed an unexpected significant change in the daily patterns of blood sugar levels in two of the patients Since there was no change in degree of control insulins were of the same batch in both trials and doses diet and amount of exercise allowed were the same it must be assumed that there was some fundamental change in the patients metabolism In a comparison of the effect of a new insulin juxtaposition of trial periods seems to be imperative since the time interval between studies may either mask or accentuate the real effect produced by an insulin

With insulin zinc suspensions the first fall in blood sugar level is observed in the early afternoon and nocturnal reactions and early morning hypoglycemia are said to be uncommon However one of the four patients in this series had to be excluded from the study because of repeated severe attacks of hypoglycemia between midnight and 3 a m

From this study it seems that insulin zinc suspensions

(7) La et 2 784 787 Oct 16 1954

as the malnutrition state needs refeeding and perhaps psychiatric management In the latter hormonal substances not only have no specific value but actually may be contraindicated as the decrease in endocrine activity appears to be an adaptive mechanism for conservation of energy necessitated by reduced caloric intake

No one laboratory test or group of tests is of definitive diagnostic significance since one or all may show impaired function in both conditions Contrariwise the presence of several normal reactions does not rule out organic disease since it is unusual to find all the endocrine glands impaired in patients with hypopituitary cachexia In the present series several patients with malnutrition showed a greater degree of impairment of endocrine function than many of those with hypopituitarism due to other causes Differential diagnosis must therefore be made by the clinician on *the basis of history physical examination and his considered judgment*

Anorexia Nervosa Endocrinologic Problem A Jores[6] (Univ of Hamburg) states that the Sheehan syndrome and anorexia nervosa are completely different entities the latter being a psychoneurosis with various signs of secondary endocrine disturbances

In 11 female patients aged 16 24 amenorrhea though present at the height of the disease was not always an early symptom In six it was preceded by anorexia It had been present from 4 to 72 months average 18 7 months All patients were considerably underweight Constipation was found in nine and vomiting in four The BMR ranging from +2 to −30% had a mean value of −20 3 Blood pressure varied between 85/65 and 110/90 with a mean of 96/63 The 11 oxysteroids were normal and the 17 keto steroids decreased (2 7 15 mg /100 ml mean 4 4 mg)

Absence of gonadotropin production decrease in thyrotropic activity and diminished 17 ketosteroid excretion would indicate decreased function of the anterior pituitary However there are important characteristics differentiating anorexia nervosa from Sheehan s syndrome namely the normal 11 oxysteroid levels and the normal insulin tolerance which do not indicate a hypofunction of the adre-

(6) A t endoc 1 17 206-210 Dec mbe 1954

those with a positive response will become diabetic by standard tests

In the discussion Frank L Engel suggested caution in interpreting results if a patient has any active illness at the time of the cortisone glucose tolerance test reporting that four hours after having given 200 mg cortisone to hospital patients without diabetes glucose tolerance was abnormal In healthy normal individuals glucose tolerance was normal after cortisone

Prognosis of Diabetes Mellitus G R Constam P Hoch strasser and F von Sinner[9] (Univ of Zurich) report that insulin antibiotics and improved control of cardiovascular

CLINICAL COURSE OF DIABETES MELLITUS IN RELATION TO DEGREE OF CONTROL

	C					
	Alw y P	Alw y Good	F	F t Poo L ter Good	F t Good L t P	T t l
No late symptoms	2	11	4	2	2	21
A few late symptoms	2	9	5	1	3	20
Many late symptoms	28	1	21	8	4	62
	32	21	30	11	9	103

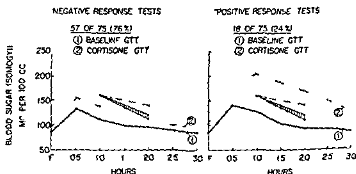
complications have prolonged the life span of diabetics con siderably Mortality is decreasing among the young and in creasing among the old diabetics Insulin has improved the short term prognosis Diabetic coma is avoidable in most instances Death is mostly due to cardiovascular changes developing after 8 20 years these late symptoms leading to a poor long term prognosis

The presence of late symptoms such as endarteritis ob literans coronary sclerosis hypertension cerebral circula tory disturbances albuminuria retinopathy and neurop athy was investigated in 103 patients with diabetes for 20 or more years Control of the diabetes was good if the blood sugar level was below 180 mg /100 ml most of the time and the urine negative for sugar and if coma occurred but once It was poor if blood sugar level was usually above 180 mg /100 ml daily sugar excretion mostly ex ceeded 30 Gm and if coma occurred several times Fair control meant alternating periods of poor and good control

(9) Schw med W b sch 84 1233 1239 Oct. 30 1954

have the same limitations as other insulins The type of insulin can influence the daily pattern of insulin activity but cannot control the extent of the blood sugar variability

✓ **Approach to Prediction of Diabetes Mellitus by Modification of Glucose Tolerance Test with Cortisone** Stefan S Fajans and Jerome W Conn[8] (Univ of Michigan) tested glucose tolerance in 152 healthy relatives of diabetic patients and 50 normal controls All persons ate a standard diet before each test Unsuspected diabetes was found in at least 19% of the 152 relatives but only 1 of the 50 controls gave a diabetic response to the glucose tolerance test



F g 110 —R spo s t co t on gl co tol r ce t t f 75 nord ab t l t e of d b t cs (C u t sy f F j S s d C J W D abet s 3 96-304 Jul A g 1954)

In 37 controls 75 nondiabetic relatives of diabetics and 18 diabetics the glucose tolerance test was repeated after 100 or 125 mg cortisone orally in an 8½ hour period before the test Striking loss of carbohydrate tolerance during the cortisone glucose tolerance test was shown by 24% of the 75 nondiabetic relatives (*Fig 110*) *1 of the 37 controls and* 10 of the 12 known diabetic patients Six obese diabetic patients lost 15 30 pounds by dieting and then exhibited normal glucose tolerance by the standard test but an abnormal response to the cortisone glucose tolerance test

The cortisone glucose tolerance test separated the nondiabetic relatives of diabetics into two distinct groups Serial studies over the coming years will determine whether

(8) Diabetes 3 296 304 July Aug 1954

dence of hypertension nephropathy etc is not greater among those who lead an irregular life indulging in ex cesses If so statistics of late complications in diabetes should be reconsidered

Problem of Diet in Diabetic Children Effect of Significant Increase in Carbohydrate on Glycosuria and Need for Insulin In a previous paper H Lestradet and A Seynaeve (Paris) presented a physiopathologic concept of diabetes not as a nutritional but as an endocrine disease requiring exclusively hormonal (insulin) treatment adjusted to constantly changing needs of the organism Study on diabetic children at a summer camp offered an opportunity to test this hypothesis

Of 33 children 15 were on a normal diet and receiving daily doses of insulin adjusted by urine examinations 5 were receiving fixed doses of insulin with practically no dietary restriction and 13 were on a restricted diet consisting of a weighed normal glucose ration in 3 and a low carbohydrate diet (80 150 Gm daily) with practically free protein and fat intake in 10 aged 8 15 At the end of the first week at camp diets were increased to 350 400 Gm carbohydrate daily for the older children and 250 300 Gm for younger ones A few dietary indiscretion occurred at first but later disappeared In 8 of 10 whose records were complete average sugar excretion for 24 hours was 20 Gm One child received a single injection of protamine zinc insulin daily two received two injections and five three injections of ordinary insulin None including these eight showed albuminuria eyeground changes or abnormal blood pressure Morning blood sugar content was between 100 and 200 mg/100 cc when glycosuria did not exceed 20 Gm One severe hypoglycemic reaction was controlled promptly Two children on three occasions had transitory acetonuria when urinary sugar content exceeded 60 Gm in 24 hours All children participated in the same activities

Results showed no correlation between glycosuria and amount of dietary glucose in subjects receiving a satisfactory dose of insulin The traditional explanation would be that by extraordinary coincidence increased glucose ration was accompanied simultaneously in all cases with im

(2) P se méd 6 707 709 M y 5 1954

Only one fifth of the eries had no late symptoms (table)

It is not so much the severity of diabetes or the type of insulin used as the age of the patient and the degree of diabetic control which determine the outcome Among 21 well controlled diabetics there was only 1 with multiple late symptoms whereas among 32 poorly controlled diabetics there were only 2 without late symptoms

So called Free Diet (Normal Diet) in Treatment of Diabetic Children G Fanconi[1] (Univ of Zurich) states that diets given after the discovery of insulin, consisting of 30 Gm carbohydrates proteins to the amount of 10% of the daily caloric intake and the rest in fats failed because they did not keep the children sugar and acetone free A diet rich in fruits and vegetables but low in proteins showed excellent early but poor late results Nephropathy developed in all of Fanconi's patients who had lived on this diet 16 or more years and none of them survived 21 years

These unsatisfactory late results thought to be caused by liver damage due to the low protein diet led to the use of the so called free or normal diet characterized by avoidance of overfeeding restriction of sugar flour and fat and intake of meat at least once a day Patients on this diet and taking insulin should not excrete more than 10% of the carbohydrate intake Acetonuria calls for increase in insulin A good indicator of efficient treatment is the blood cholesterol level Hypercholesteremia indicates mistakes in insulin dosage or in diet

Since 1946 17 of Fanconi's patients have received this normal diet Three could reduce their insulin five had to increase it and nine needed the same amount as before Growth and weight gain were accelerated in most instances incidence of coma and precoma decreased by 50% and no kidney or funduscopic changes were found thus far The number of necessary office visits also decreased

The statistics of Keiding Root and Marble reveal an incidence of late nephropathy of 28% in poorly controlled patients and none in the well controlled It should be considered however that well controlled diabetics usually care for their health and avoid excess in every respect It would be interesting to study whether in nondiabetics the mu

(1) Schwei z m d Wchnsch 85 577 Jn 2 1955

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[2] Sem med 62 707 09 M y 5 1954

provement exactly proportional to the carbohydrate supply or at least that increasing the glucose ration would be sufficient to increase tolerance and therefore ameliorate the disease The facts indicate that insulin treatment adjusted according to results of two or three urinalyses daily is sufficient for control of juvenile diabetes

Diabetic Nephropathy and Retinopathy Jan Muri[3] (Norway) reviewed case histories of 269 patients treated in the Oppland County Hospital Norway for diabetes during 1939 51 In the 84 patients who developed diabetes before age 50 average duration of the disease was 15 6 years Only 72 of these were traced 5 of whom had died All were found to use insulin and were poorly controlled Seventeen had nephropathy and/or retinitis in 53 (63%) the eye grounds and urine were unremarkable Frequency of complications increased with duration of disease The age when diabetes was first diagnosed was not important and the history of acidosis did not appear to have a significant bearing on development of complications None of the patients had serious diabetic neuropathy

The low frequency of retinopathy and nephropathy among the poorly controlled diabetics in Oppland County suggested that diabetic complications can arise from factors other than poor control namely constitutional and/or environmental influences The inhabitants of this region were considered to be calm well balanced even tempered people whose existence was devoid of the stresses connected with modern living The author concluded that little could be gained by burdening these particular patients with rigid diabetic control

Although the importance of control seemed evident from the investigations of Joslin it was thought that a protected and unconcerned life might have played a part in the good result The 23 Victory Medal winners in Joslin s series all lived in unusually favorable homes and in comfortable social circumstances

[There is now general agreement about all facets of diabetic management except the question of whether tight control prevents the development of late complications The preceding four papers present apparently conflicting data on this subject It is worth emphasizing however that Fanconi s free diet is *not* an unsupervised diet and that Lestradet

(3) Act m d scand a 149 11 219 1954

attempted to reduce the glycosuria of his patients by manipulating the insulin dosage. Fanconi's and Muri's criticisms of the inadequacy of the control observations presented by the Joslin Clinic deserve especially serious consideration.—Ed.]

Effect of Kimmelstiel Wilson Syndrome on Insulin Requirements in Diabetes was described by John W Runyan Jr David Hurwitz and Stanley L Robbins[4] who reviewed the clinical and pathologic records of 375 patients with diabetes mellitus who came to autopsy between 1940 and 1952 Of this group 138 had Kimmelstiel Wilson renal lesions

The study was limited to 106 patients who had had diabetes for three years or more and been on insulin for at least eight consecutive months and whose records contained the necessary data for evaluation There were 54 with and 52 without Kimmelstiel Wilson lesions Both groups were comparable in age at death duration of diabetes and insulin requirement during basal and preterminal periods Fifteen patients required no insulin before the terminal admission 5 with and 10 without proved Kimmelstiel Wilson lesions Acidosis did not develop in any of these The clinical syndrome of Kimmelstiel and Wilson—edema albuminuria and hypertension—occurred about 3½ times more frequently in the group with the proved renal lesions

A decrease in insulin requirement was noted in most patients with the clinical syndrome regardless of the eventual pathologic classification of renal lesions Increases in insulin requirement occurred in some with Kimmelstiel Wilson lesions The net result was an over all decrease of only 2 units in mean daily requirement Similar increases and decreases occurred in patients without the lesions

In five patients detailed dietary histories indicated a marked decrease in food intake with onset and progression of the syndrome It is well established that dietary restriction promotes increased carbohydrate tolerance Since edema was present in 59% of the group with and 21% of those without Kimmelstiel Wilson lesions loss of body fat and lean mass could have taken place without changes in total body weight Decreased food intake may be an important factor in many patients with otherwise unexplained

(4) New England J Med. 252 388 391 M 10 1955

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(3) Acta med scand 149 211 219 1954

ing life they had had severe edema hypertension proteinuria and uremia Lesser degrees of nodulation were found in four patients who had minimal sclerotic changes and who had had no albuminuria edema or hypertension ✓ It was concluded that the marked edema in Kimmelstiel Wilson s disease without cardiac failure was associated with glomerular nodulation combined with arteriolosclerotic nephritis

Hypophysectomy in Man Experiences in Severe Diabetes Mellitus R Luft H Olivecrona and B Sjogren[6] (Serafimer Hosp Stockholm) performed hypophysectomies on nine patients with severe diabetes mellitus and progressive malignant vascular complications Two were followed for only two months The others (three men and four women) were aged 24 30 at the time of operation and had had diabetes 14 20 years All seven had progressive impairment of renal function and diabetic retinopathy All but one had almost total amaurosis Cortisone was given on the day of operation and in gradually decreasing doses for one month postoperatively The main postoperative complications consisted of severe hypoglycemia in three patients intracranial hematoma in one epileptic seizures in four infections in two marked anemia in four and anorexia and vomiting in two

In all patients 17 ketosteroid excretion fell to low or zero values within three to six weeks after operation The BMR became subnormal in all and radioiodine tests showed no thyroid clearance Results of renal function tests were the same before and after surgery There was no change in vision or in the extent of eyeground or cataract abnormalities In four patients the daily insulin requirement before hypophysectomy ranged from 24 to 60 units After hypophysectomy one patient required no insulin one needed only 6 units and the other two required only 8 units of protamine zinc insulin daily Two patients died within 24 hours of operation two died within 5 months of surgery one was alive 2½ years and two were alive 1 year after hypophysectomy

[The desperate plight of patients with advanced vascular complications of diabetes has prompted several physicians to attempt heroic therapy Kinsell has reported briefly on hypophysectomy for this condition in four

(6) J Clin E doc 1 15 391-408 Ap 1 1955

amelioration of diabetes and would not be evident from clinical records Diabetic acidosis occurred at least as frequently in patients with Kimmelstiel Wilson lesions as in those without Four patients with far advanced renal changes had diabetic acidosis as a terminal event

There was no evidence to support the thesis that a specific type of diabetes characterized by amelioration of the disease and infrequent occurrence of acidosis is associated with Kimmelstiel Wilson renal lesions per se

[This study contradicts the common statement that after patients develop the Kimmelstiel Wilson syndrome they require less insulin and have less severe diabetes —Ed]

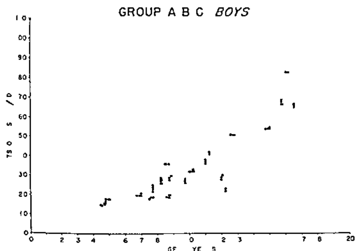
Clinical Features Associated with Kimmelstiel Wilson Lesions George W Dana and Charles G Zubrod[5] (Johns Hopkins Univ) reviewed the clinical findings in all patients with diabetes mellitus on whom autopsy was performed between 1938 and 1951 There were 45 patients with Kimmelstiel Wilson nodules in the glomeruli and 133 without nodules There was no significant difference between the two groups in the age at onset of the diabetes or in its duration except that patients who had diabetes for less than five years rarely had nodules at autopsy Development of nodules could not have been due to duration of diabetes alone since 29 patients who had diabetes for 11 years or longer had no glomerular nodules Diabetic retinitis was present in 35 of the 45 patients with nodules but in only 12 of the 133 controls The combination of retinitis and peripheral edema present in only *2%* of the controls but in 60% of those with glomerular nodules was considered a valuable diagnostic aid The classic triad of hypertension albuminuria and edema occurred in less than half the patients with Kimmelstiel Wilson lesions but when present strongly suggested the diagnosis There was no single clinical characteristic which could set apart patients with glomerular nodules Dilation of glomerular capillaries similar in appearance to retinal aneurysms was noted in 11 patients with nodules

Glomerular nodules occurred with and without arteriosclerotic and arteriolosclerotic nephritis The six patients with the most marked glomerular nodulation had extensive arteriosclerotic and arteriolosclerotic nephritis Dur

(5) B ll J h s H pk Ho p 95 338 346 Dec mb 1954

catabolism it can function as a growth hormone in the absence of pituitary factors

Insulin Requirements of Children with Diabetes Mellitus Maintained in Good Control Helen G Kelly P Tirumala Rao and Robert L Jackson[8] (State Univ of Iowa)



Fg 111—S tt g m f y g in In q m t of ll g g p f b y f m f y t d lthood (Court y f K lly H G t l A M A Am J D Child 89 31 41 F bru y 1955)

studied serial insulin requirements and growth of 48 well controlled juvenile diabetics Patients were considered in good to excellent control if urine specimens were free from sugar except for occasional traces and there were only rare mild insulin reactions Most patients were classified as in very good to excellent or good control They were grouped according to year of onset 0 5 years 6 10 years and 11 15 years All made normal progress in height and weight

Under 10 years in both boys and girls there was no marked difference in insulin requirement which could be related to age at onset of diabetes Whether the diabetes began before age 5 or between 6 and 10 years daily insulin needed at a given age was about the same Insulin requirement increased in a uniform manner to age 10 After

(8) A M A Am J D Ch ld 89 31-41 F bru ry 1955

additional cases (Diabetes 3 358 366 September 1954) and Wortham and Headstream (ibid pp 367 373) and Martin and Wilson (ibid pp 375 382) present data on eight cases treated with bilateral adrenalectomy In all of these patients the vascular disease was so far advanced that little improvement could have been anticipated This type of treatment deserves further study but only in restricted experimental situations where careful follow up is possible At present it is not recommended as a routine method of treatment —Ed.]

Effect of Insulin on Nitrogen Retention in Hypophysectomized Rat was described by R T B Lawrence James M Salter and Charles H Best[7] (Univ of Toronto) Two experiments were performed on male hypophysectomized rats maintained in a constant temperature room at 28 C In experiment A the daily nitrogen balance in six untreated hypophysectomized rats was determined for a 12 day period In experiment B hypophysectomized rats were divided into a control group of 12 animals and an experimental group of 8 Indications of the nitrogen balance in the controls were secured by determining changes in the nitrogen content of their carcasses Six of the rats were killed on the initial day of the experiment and their average total body nitrogen compared with a similar value obtained from the remaining six controls killed on the last day of the experiment

The daily nitrogen balance of each of the eight rats in the experimental group was determined for (a) an initial period of three days before insulin was administered (b) an intermediate period of seven days during which each rat received one daily injection of increasing amounts of protamine zinc insulin and (c) a four day period following cessation of insulin treatment The rats were killed with surviving members of the control group on the fourteenth day

In experiment A untreated hypophysectomized rats remained in nitrogen equilibrium A similar effect was noted in the control group of experiment B The insulin treated hypophysectomized rats however showed an increase in the absolute amount and the percentage of nitrogen retained

The acquired data suggest that a linear relationship may exist between insulin dosage and nitrogen retention It was concluded that since insulin stimulates utilization of amino acids and synthesis of proteins and inhibits protein

(7) Brit. M J 2 437-439 Aug 21 1954

treatment was most decisive in keeping down the amount of water Factors other than lowering of the blood sugar level were thought to play a role since no close relationship could be demonstrated between amount of water and mean blood sugar level during pregnancy No significant correlation was found between amount of amniotic water and duration of diabetes Further there was no correlation between hydramnios and diabetic retinitis toxemia fetal mortality or birth weight (2 600 5 000 Gm)

Experimental and Clinical Significance of Chorionic Gonadotropin Assays is discussed by J A Loraine[1] (Univ of Edinburgh) The assay dependent on enlargement of the prostate in immature rats is a convenient method for quantitative estimation of chorionic gonadotropins in the blood urine and placentas of patients In the first trimester of normal pregnancy very high readings e g 20 000 50 000 I U were obtained for urinary excretion (I U /24 hours) and serum concentration (I U /L) but in the second and third trimesters they were in the range of 4 000 11 000 I U Values consistently outside this range were regarded as pathologic

In severe pre eclampsia mean figures for urinary excretion and serum concentration of chorionic gonadotropins were significantly higher than those in normal pregnancy In mild and moderate pre eclampsia and in essential hypertension associated with pregnancy the figures did not differ significantly from those in normal pregnancy In all cases mean renal clearance of chorionic gonadotropin was less than 1 ml /minimum In normal and diabetic pregnancies constant figures were obtained in the three trimesters Mean clearance in severe pre eclampsia was significantly lower than that in normal pregnancy

Of 44 pregnant diabetics tested only 12 had abnormally high chorionic gonadotropin excretion Serum concentrations measured in 35 were abnormally high in only 8 Stilbesterol administered to either normal or diabetic women produced only an evanescent fall in urinary excretion of chorionic gonadotropins No correlation was seen between urinary excretion and serum concentration of chorionic

(1) Ann b t gyn ec Fen 4 129 140 19 3

age 10 insulin requirement in girls increased rapidly, concomitant with the prepubescent growth spurt then decreased after the period of rapid growth In boys the rapid increase in insulin requirement coincided with the prepubescent growth spurt after 12 and decreased slowly as adulthood was reached (Fig 111)

A knowledge of insulin requirements and growth characteristics at different ages in well controlled diabetic patients is essential to maintenance of good control and normal growth

[The growth promoting properties of insulin are sometimes lost sight of because of its major carbohydrate effect Whether the protein anabolic effects are mediated through changes in carbohydrate metabolism or are a direct effect of the hormone normal growth is impossible in the absence of insulin This and the preceding article emphasize the fact that the insulin requirement increases as growth progresses In the diabetic child therefore frequent readjustment of insulin and dietary allowances are necessary to permit normal growth —Ed]

Hydramnios in Diabetics Amount of Amniotic Fluid in Relation to Treatment was studied by Jørgen Pedersen and Gunnar Jørgensen[9] (Copenhagen) The volume of amniotic fluid present at delivery was estimated in 100 out of 149 pregnant patients with diabetes The subjects were divided into two groups on the basis of long term and short term treatment according to the time they were first seen by a physician during their pregnancy Nondiabetic controls were studied to estimate the amount of water normally present at delivery Since in 24 cases amounts over 975 ml were not found the term hydramnios was reserved for cases in which volumes over 1 000 ml were recorded

The incidence of hydramnios was 50% (greater than 1 000 ml) and 20% (greater than 1 500 ml) as determined by the present method which consisted of puncturing the membranes with a catheter and collecting the waters with collection again at delivery and estimation of loss A significant difference was noted in the amount of water between long term treated and short term treated patients In the former the average was 928 ml and in the latter 1 454 ml in a special series

It was thought probable that this difference was due to the different length of treatment in the two groups However it was not possible to demonstrate which part of the

(9) Acta endocrinol 15 333 341 Apr 1 1954

hypothesis that normal transport of lipid substances is from higher to lower S_f classifications and suggesting that diabetic acidosis interrupted the transport with resultant accumulation of high S_f lipoproteins Treatment probably released the block and measurable increases in the lower classifications were observed Abnormalities in lipoproteins in diabetic acidosis were so diffuse and regular that they were believed to be a contributing factor in the premature atherosclerosis of diabetic patients

Bone Changes in Diabetes William A Copland[3] (United Bristol Hosp) made x ray studies of diabetics with symptoms or signs referable to the feet Of 50 patients examined 19 had bone changes representing an incidence of about 5% of the 400 patients attending the diabetic clinic at the time The osseous changes predominated in older patients with ages ranging from 53 to 74 The classic features of Charcot joint were not seen All patients had or had had an inflammatory lesion usually a perforating ulcer near the site of the affected bone Others especially if the phalanges were involved had or had had a septic corn or diabetic cutaneous gangrene

Inflammation due to acute or low grade soft tissue infection begins near a bone often near the joint Osteoporosis is the first sign A break then occurs in the cortex usually in the neck of the affected metatarsal or phalanx and osteitis ensues If the condition heals a periosteal reaction is seen along the shaft and the affected bone may be repaired Usually however the head of the bone is gradually destroyed the shaft being attacked next and the medulla progressively destroyed resulting in a taper or pencil appearance (Fig 112) Appearances vary with virulence of the infection and the patient s resistance The destructive inflammatory process may be arrested at any stage except in neuropathic joints and is significant in differential diagnosis Destruction may advance to extremely gross disorganization

Although there is no reason why true Charcot joint should not develop in a diabetic with neuritis most bone changes commonly seen in this condition though influenced by poor blood supply lack of sen ation and possibly the

(3) P oc R y Soc M d. 47 34 347 M y 1954

gonadotropins and the medical and obstetric observations

It is suggested that discrepancies with observations by other investigators on the significance of elevated chorionic gonadotropin titers in pregnancy and the effects of stilbestrol can be attributed to the methods of assay employed The corpora lutea method is highly subjective with a large statistical error and estimation of the gonadotropin in rat units is unsatisfactory Comparison of results obtained by the corpora lutea and prostatic weight methods using the international standard preparation might be illuminating

[This careful study gives no support to the concepts of altered hormonal response of pregnant diabetics propounded by Dr Priscilla White (e g Am J Med 7 609 1949) which forms the justification for the hormonal treatment" of pregnant diabetic women —Ed.]

Effects of Diabetic Acidosis and Coma on Serum Lipoproteins and Cholesterol were studied by Elizabeth F Tuller George V Mann Fredy Schertenleib Charles B Roehrig and Howard F Root[2] (Boston) in 18 patients 6 with diabetic acidosis and 12 in diabetic coma Though no precise correlation was observed between blood sugar or carbon dioxide values and either cholesterol or lipoprotein values a general relation between degree of acidosis and serum lipid deviation was noted Treatment of acidosis resulted in rising carbon dioxide and falling serum lipoprotein and cholesterol levels In the 24-48 hours after first oral feeding the fractions S_f 21 100 and 100-400 increased in concentration In some patients the increase was maintained in others the fractions later returned to normal On admission the patients with acidosis had serum cholesterol levels between 153 and 325 mg /100 cc and lipoprotein levels of 120 310 mg S_f 0-11 40-143 mg S_f 12 20 95-452 mg S_f 21 100, and 0 100 mg S_f 100-400 The patients in diabetic coma had 78-490 mg /100 cc S_f 0 11, 46-170 S_f 12 20 70 1 420 S_f 21 100 and 14-400 S_f 100-400 and cholesterol levels between 206 and 664 mg /100 cc After treatment the values for cholesterol and the various lipoproteins did not return to normal at the same rate Thus the changes were considered real and not artefacts due to hydration In one patient the S_f 20-400 lipoproteins were reduced by 90% while the S_f 0 20 group increased by 14% supporting the

(2) Diabetes 3 279 286 July Aug 1954

five patients manifesting local reactions to insulin were also performed

The skin reactions in patients exhibiting local reactions to insulin were no different from those in the control group The Prausnitz Kustner passive transfer phenomenon was ab ent in all five instances It is concluded that local nod ules with or without stinging or erythema observed in patients receiving insulin therapy are not due to any anti gen antibody mechanism

Dermal Reactions to Insulin Therapy Ronald G Paley[5] (Univ of Leeds) tested dermal reactions to insulin therapy in two groups of diabetics One group consisted of 11 pa tients who had active local reactions to therapeutic injec tions of insulin not due to faulty technic The other group of 18 had never received insulin and acted as controls Each patient received a 0 02 ml intradermal injection of test solutions British soluble insulin with phenol preserva tive British soluble insulin with cresol preservative and two types of American soluble insulin each produced signif icantly larger areas of reaction in patients who had expe rienced local reactions to insulin than were produced in patients who had never received insulin Such sensitive patients were considered ideal for experimental testing

A British experimental soluble insulin a Danish insulin zinc suspension and three types of British insulin zinc sus pensions were tested All induced skin reactions comparable to those seen with the original test solutions except British insulin zinc suspension with cresol BP 0 2% as a preserva tive which produced a significantly smaller skin reaction When commercial soluble insulin had been recrystallized six times a strikingly significant reduction in the mean area of the skin reaction had been observed Efforts to obtain impure dermal reacting factor by various physico chemi cal procedures proved fruitless

Significant differences in skin reaction to various batches of the same soluble insulin previously noted were observed in this experiment with new insulin zinc suspensions

It was predicted that cutaneous reactions will develop with the new insulins and that variations of these reactions

(5) La t 2 1249 1250 Dec 18 1954



Fg 11 —X ys taken 1949 1950 a d 1953 show g h onc low grad ste t w th p g e tap g f sh ft Note p f t g ulce bel w d metata sal h d b g ng t t m f fi t x y Last x y how w rt f m g ou d di tal e d f met t sal (Cou tesy f Copland W A P oc R y Soc Med 47 345 347 M y 1954)

abnormal metabolism of diabetes are due to an inflammatory process This explanation applies to a variety of conditions affecting the extremities in which cutaneous lesions are open to infection

[The term Charcot joint is sometimes applied to the bone changes in these patients (Antes J A M A 156 602-603 Oct 9 1954) with the implication that the changes are of neuropathic origin (Miller and Lichtman A M A Arch. Surg 70 513 518 April 1955) The primary infectious nature of most of the lesions as described by Copland is more in keeping with our experience Probably the neurologic lesions permit osteomyelitis to progress farther without treatment than would be possible in patients with normal sensory function —Ed]

Sensitivity Tests to Insulin in Patients with Local Skin Lesions from Insulin were conducted by Maxwell L Gelfand Maximilian Fabrykant and Benjamin I Ashe[4] (New York Univ) Sixteen diabetic patients exhibiting local skin reactions to insulin as nodules with or without erythema or stinging were tested intradermally with various insulin products beef and pork protein The same number of non diabetics not using insulin were similarly tested with the same substances Passive transfer tests with the serums of

(4) P oc Soc E per B 1 & Med 86 58 261 J e 1954

role of growth hormone in diabetes was indirect although there is evidence that growth hormone is diabetogenic in carnivorous animals

It is assumed that the growth hormone was important in insulin resistance The patient was above average height at onset of diabetes and grew rapidly

Impaired Glucose Tolerance a Consequence of Excessive Carbohydrate Consumption Samuel Alpert[7] (V A New York) reports a case

Youth 19 with abdominal pain of several hours duration was found to have glycosuria and acetonuria He had no history of poly dipsia polyuria or weight loss He had always been fond of sweets and in the military service consumed daily an average of 24 choco late bars two or three glasses of malted milk and several bottles of soda pop in addition to three generous meals Weight remained constant at 170 lb and he was 72 in tall Blood sugar was 140 mg / 100 cc He was placed on a dietary regimen and insulin and im proved progressively Insulin was discontinued one year later because of aglycosuria A standard oral glucose tolerance test revealed 167 mg / 100 cc blood sugar at two hours and 145 mg at three hours A year later a repeat tolerance test was normal and the diagnosis of diabetes mellitus was withdrawn The patient promptly resumed his old gluttonous habits which he maintained for the next two years His estimated daily intake was 7 000 calories of which 4 000 were derived from carbohydrate sources Weight re mained unchanged A glucose tolerance test showed 242 mg blood sugar at two hours and 229 mg at three hours with glycosuria. A new diet was prescribed After 5 months the tolerance test was only mildly abnormal and after 11 months on the diet it was within normal limits There was no further contact with the patient

It was postulated that the disturbance of glucose metabo lism resulted from islet exhaustion induced by excessive consumption of carbohydrates The capacity to maintain a normal blood sugar level was repeatedly overwhelmed by rapid absorption of large amounts of glucose from the in testinal tract causing a recurrent hyperglycemic state This gave rise to degenerative changes in the pancreas pre sumably not beyond the degranulation stage since reversi bility of the clinical picture was twice demonstrated This case could not be regarded as a true example of diabetes mellitus nor could its development be regarded as related to the usual pathogenesis of the disease

(7) A I t. M d 42 927 931 April 1955

will be observed between one batch of insulin and another

[Paley by measuring the area of the skin reaction was able to demonstrate differences not appreciated by the Gelfand qualitative appraisal (preceding article) In both series however both the patients with skin sensitivity and the control subjects had dermal reactions The nature of the material causing these manifestations deserves further investigation it is probably not insulin itself since repeated recrystallization reduced the severity of the skin reaction without reducing the potency of the insulin —Ed]

Insulin Resistance Douglas Hubble[6] reports a high degree of insulin resistance in an adolescent girl which appeared to follow a phasic pattern related to the menses The resistant phases were usually premenstrual and the sensitive phases postmenstrual

Girl 13 hospitalized for diabetic ketosis had had symptoms of diabetes for two months She was 5 ft 4¾ in tall 4 in above the average for her age She required 48 units of soluble insulin daily During the ensuing year the insulin requirement increased to 60 units of soluble insulin daily Height had increased by ¾ in and she weighed 121 lb Secondary sex characteristics were fully developed but the menses had not begun While she was hospitalized for insulin restabilization persistent hyperglycemia developed and despite steady increases of insulin to 12 160 units daily the blood sugar level was seldom below 250 mg/100 ml during the day Intravenous insulin only temporarily reduced the hyperglycemia During one period of acidosis and ketosis the blood sugar level was 75 mg She was treated with saline intravenously gastric lavage and small doses of soluble insulin Insulin sensitivity was restored and she was maintained on 52 units of soluble insulin daily for two weeks when hyperglycemia precoma and insulin resistance reappeared Three episodes of insulin resistance developed in the following three months During the last episode slight vaginal hemorrhage appeared for the first time and menstruation was fully established for two days on recovery Thereafter she had six episodes of insulin resistance which were most severe during the menses Variable periods of insulin sensitivity followed each menstrual period The largest amount of insulin given was 19 200 units in one day Her course was complicated by thrombophlebitis urticaria and multiple abscesses at the sites of insulin injection. The patient died in renal failure and anuria after intravenous insulin therapy totaling 18 000 units in one day

There can be little doubt that the insulin resistance was hormonal and related to the premenstrual phase of the cycle Urinary output of sex hormones was not increased and there was no correlation between variations in estrogen and pregnanediol excretion and insulin needs No assay of growth hormone was available Clinical evidence for the

(6) Brit M J 2 10 10 4 Oct 30 1954

mone alone The greatest fall in phosphate excretion after calcium infusions occurred in patients with osteomalacia all assumed to have secondary hyperparathyroidism Patients with hypoparathyroidism had an increase in phosphaturia after calcium infusions which would be expected in the absence of changing parathyroid function

Other investigators have not observed similar results probably because amounts of calcium used were inadequate Changes in phosphate excretion are too small to account for rises in serum phosphate It has been suggested that parathyroid hormone drives phosphorus into cells which might explain the discrepancy Since patients with hypoparathyroidism had increased serum phosphorus after calcium infusion perhaps hypercalcemia alone had a similar effect

[Schaaf and Kyle (Am J M Sc 228 262 September 1954) have used similar criteria for the diagnosis of hypoparathyroidism The advantage of the Cp/Ccr ratio is that it cancels out mathematically the factor of urine volume so that completeness of collection of urinary specimens is not a factor in the accuracy of the test Cp/Ccr is calculated as (Up×Pc)/(Ucr×Pp) where Up is urinary phosphate concentration Pc plasma creatinine concentration etc —Ed]

Roentgen Recognition of Parathyroid Adenoma Stanley M Wyman and Laurence L Robbins[9] (Massachusetts Gen l Hosp) report that of 34 surgically proved parathyroid adenomas 20 could be localized roentgenologically Examination should be as complete as possible and should include roentgenoscopy spot x rays with barium in the esophagus and large conventional x rays of the chest and lower neck Minimal changes in the outline and course of the trachea or esophagus may be of major importance Well grounded knowledge of normal roentgen anatomy is essential Plain anteroposterior and lateral x rays of the neck without contrast substance in the esophagus may be informative

The most significant finding i e the outline of a soft tissue mass is rarely seen In most cases only secondary evidence is available—indentation of the esophagus trachea or both The degree of deformity or displacement of these structures depends on size and location of the tumor Occasionally a tumor attains such size and extends low enough into the thorax to be outlined laterally by adjacent lung In one third of the cases in which the parathyroid adenoma

(9) Am J Roentg 71 777 784 May 1954

CALCIUM PHOSPHORUS AND THE PARATHYROID GLANDS

Effect of Intravenous Calcium on Phosphate Excretion was studied in 10 patients with osteoporosis 7 with generalized bone rarefaction and steatorrhea and 14 with no bone disorders by B E C Nordin and Russell Fraser[8] (Postgraduate Med School London) Of the patients with osteoporosis one had Cushing s syndrome and nine had no other disease or metabolic abnormality All received diets containing 100 mg calcium and 500 700 mg phosphorus/day Test calcium was administered intravenously as gluconate 15 mg/kg body weight Urine samples were collected every 2 or 4 hours for 24 hours In each experiment creatinine clearances and phosphate creatinine clearance ratio (Cp/Ccr) were determined The ratio estimates changes of tubular phosphate reabsorption

Calcium given intravenously raised the serum calcium and serum phosphorus levels in all groups but the increase was least marked in patients with osteomalacia Patients with no bone disorders and those with osteomalacia had a concomitant fall in hourly phosphorus excretion and decrease in Cp/Ccr The patients with osteoporosis had no change in phosphate output and little change in Cp/Ccr Similar tests in two patients with hypoparathyroidism induced a rise in serum phosphorus level, Cp/Ccr and urinary phosphate excretion Low phosphate clearance with rise in serum phosphorus indicated an increase in tubular reabsorption of phosphate despite increase in tubular phosphate load

In normal subjects high serum calcium probably depressed parathyroid activity, thus increasing renal tubular reabsorption of phosphate and serum phosphorus and decreasing urinary phosphorus Parathyroid hormone administration increased phosphate excretion and the effect was greater after calcium infusion than after parathyroid hor

(8) Cl n Sc. 13 477-490 N embe 1954

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(9) Am J Roentgen L 71 777 84 My 1954

was recognized, the indentation or displacement involved the trachea alone in one third, the esophagus alone and in one third both trachea and esophagus Of the 14 adenomas not recognized roentgenologically 8 measured 1 cm or less in maximal diameter It is believed that tumors measuring less than 1 cm are not likely to be visualized Most of the recognized tumors were estimated to measure 3 cm in diameter

[The roentgenologist may be of considerable help in localizing the parathyroid adenoma but only after the existence of this abnormality has been proved clinically All that the x rays can do is demonstrate a mass they cannot define its nature—Ed]

Primary Hyperparathyroidism Observations in Series of 50 Cases were made by John Hellstrom[1] (Karolinska Inst) Thirty three patients were women The youngest was 16 and the oldest 62 Average age was 46 roughly the same for men and women Distribution of the two most striking lesions of hyperparathyroidism osteitis fibrosa generalisata and renal calcification was as follows skeletal changes 13 patients renal changes 27 both skeletal and renal changes 10

Duration of symptoms was five years or more in 50% of the subjects The following symptoms were present alone or combined with others

Skeletal symptoms	
Bone and joint pain	14
Fractures	9
Giant cell tumor	8
Renal symptoms	
Calculi	27
Infection in urinary tract	15
Polyuria polydipsia	3
Other symptoms	
Hypertension	10
Abdominal and intestinal disorders	9
Headache	8
General fatigue	5
Endocrine disorders	3

In five of the eight patients with giant cell tumors these were localized in the jaws and were for varying periods treated as a local process until they were recognized to be a part of the general skeletal disease Symptoms of urinary tract infection usually accompanied symptoms of renal

(1) A ta endocrin l 16 30 58 M y 1954

calculus but in some instances appeared later and in others much earlier In three cases there were marked polyuria hyposthenuria and polydipsia before renal calcification was demonstrable on x ray Hypertension was moderate and transitory in early cases but severe and stationary in the more advanced cases An increased incidence of duodenal ulcers was observed in this series

A high calcium and low phosphorus content of the blood and elevated calcium levels in the urine were thought to be suggestive of hyperparathyroidism but not pathognomonic and were greatly dependent on the status of kidney function

The pathologicoanatomic basis of hyperparathyroidism in most cases was an adenomatous transformation of only one parathyroid gland In 14% there was primary hyperplasia of all the glands Duration of symptoms was not dependent on size of the adenoma or on its content of wasserhelle cells In cases with renal changes small adenomas with a high content of wasserhelle cells predominated and in those with skeletal changes large adenomas with a low content of wasserhelle cells High blood calcium values were more common in the latter

Coexistent changes in the thyroid glands were present in 41% of cases usually in the form of small adenomas but also as nodular or diffuse goiters

Primarily because of renal damage hyperparathyroidism should be treated surgically as soon as diagnosis is made In cases of single adenomas the disturbed calcium metabolism as a rule returns rapidly and permanently to normal and the patient becomes symptom free However in many cases the prognosis is poor because of permanent renal damage and hypertension In diffuse hyperplasia it is usually impossible to bring about complete regression of hypercalcemia although the patient s general condition may improve

Differentiation of Hyperparathyroidism and Milk Alkali (Burnett)—Syndrome Laurence H Kyle[2] (Georgetown Univ) emphasized the difficulty in differentiating hyperparathyroidism from the milk alkali syndrome

CASE 1—Man, 49 with pruritus for 2½ years a 30 lb weight

(2) New E gla d J Med. 26 1035 1040 December 1954

loss increasingly severe generalized muscular weakness and severe polydipsia and polyuria for 20 years had been taking an average of 226 Gm. bicarbonate of soda and 2 3 L milk daily to control epigastric pain of peptic ulcer Physical examination was noncontributory Urine specific gravity was 1 005 1 011 pH 7 7 5 albumin 2 3+ and 24 hour calcium excretion 38-110 mg /100 ml Hematocrit was 25% hemoglobin 8 3 Gm /100 ml and red blood cell count 2 900 000 There were marked azotemia elevated blood bicarbonate level hypercalcemia and hyperphosphatemia X rays of the orbits revealed bilateral annular calcification. Treatment with increased fluids and low calcium acid a h diet reduced the nonprotein nitrogen slightly Calcium level returned to normal and the serum phosphorus was lowered slightly

Four months later there was a considerable rise in nonprotein nitrogen CO combining power was in the acidotic range and hypocalcemia and hyperphosphatemia were marked Alkaline phosphatase previously normal was 22 Bodansky units At autopsy a congenital horseshoe kidney marked hydronephrosis severe nephrocalcinosis and widespread metastatic calcifications were found. There was a large duodenal ulcer crater No parathyroid glands were seen

CASE 2—Man 42 with abdominal pain and vomiting had a 17 year history of recurrent symptomatic urinary calculi with two nephrostomies He had ingested 1 2 L milk daily since childhood and for 20 years had taken large amounts of bicarbonate of soda calcium carbonate and magnesium carbonate daily for chronic indigestion Physical examination was noncontributory No calcifications were seen on slit lamp examination Urine specific gravity was 1 005 1 009 pH 7 7 5 and 24 hour calcium excretion 86-262 mg He had hypercalcemia slight hyperphosphatemia normal alkaline phosphatase hypochloremic alkalosis and moderate azotemia He improved on a low calcium diet and fluids intravenously A calcium infusion test produced an increase in the 24 hour urinary phosphorus and a minimal increase in serum phosphorus typical of the response in hyperparathyroidism On exploration an adenoma of mixed type was found and excised and improvement followed Serum calcium level was 10 8 mg and phosphorus 5 mg /100 ml one month after operation

A history of milk alkali ingestion is necessary for diagnosis of milk alkali syndrome but does not exclude hyperparathyroidism Peptic ulcer is frequent in hyperparathyroidism and epigastric discomfort even more common often leading to self medication with antiulcer therapy If the hyperparathyroidism produced severe azotemia there would be normal or even increased serum phosphorus without hypercalciuria Demonstrable bone disease or increased alkaline phosphatase would not be present if enough cal

cium were ingested to prevent skeletal changes Calcinosis and band keratopathy could occur in any type of hypercalcemia but absence of ocular calcification would be strong evidence against the milk alkali syndrome The most striking finding in this syndrome is a mild alkalosis in contrast to the severe acidosi usually present in patients with comparable azotemia from other causes If irreversible kidney damage has not occurred a diet low in calcium and absorbable alkali should improve the laboratory findings

Of several features that suggest the milk alkali syndrome the combination of azotemia and alkalosis is most important Although response to dietary correction is most helpful in diagnosis the presence of irreversible renal failure may necessitate histologic examination of parathyroid tissue Data indicate that this syndrome occurs because of renal impairment secondary to alkalosis combined with increased intake and decreased excretion of calcium

Idiopathic Hypoparathyroidism Study of Three Cases P K Robinson E Arnold Carmichael and J N Cumings[3] (London) conducted calcium and phosphorus balance studies over a three month period in three patients with spontaneous parathyroid deficiency

Case 1—Man 31 had occasional convulsive attacks laryngeal stridor carpopedal spasm cramps in the legs and paresthesias in the fingers The skin was dry nails brittle and cracked and teeth cariou and hypoplastic Chvostek and Trousseau signs were present The left arm and leg were ataxic and left plantar response was extensor Position and vibration sense were impaired Bilateral lenticular opacities were present Serum calcium level was 4 8 mg / 100 ml phosphorus 6 6 mg and alkaline phosphatase 12 2 King Armstrong units A skull x ray revealed calcification in the basal ganglions An intravenous pyelogram showed a functioning right kidney There was little clinical improvement after two courses of parathyroid hormone although Chvostek and Trousseau signs disappeared Dihydrotachysterol produced subjective improvement biochemical abnormalities were reversed and he became asymptomatic

Case 2—Woman 28 complained of carpal spasm general body stiffness and difficult breathing for 10 years Her vision was impaired but no cataracts were present Chvostek and Trousseau signs were easily elicited X rays of the skull revealed calcification of basal ganglions and dentate nucleus Serum calcium level was 6 mg / 100 ml phosphorus 5.28 mg and alkaline phosphatase 7 King Armstrong units Dihydrotachysterol produced clinical im

(3) Q rt J M d 9 383-40 O t be 19 4

provement and serum calcium and phosphorus levels became normal

CASE 3—Man, 59 with signs of mental deterioration for five years had clonic movements of the legs and carpal spasm Chvos tek s sign was absent and Trousseau s sign present He had cataracts and calcification of the basal ganglions a masklike facies and an attitude of flexion Serum calcium level was 6 8 mg/100 ml phosphorus 5 1 mg and alkaline phosphatase 6 4 King Armstrong units Dihydrotachysterol produced some improvement

A constant diet containing 750 1 000 mg calcium and 800-1 100 mg phosphorus daily was fed to the subjects and urine and stools examined for calcium and phosphorus The Ellsworth Howard test (injection of 30 BP units of parathyroid hormone intravenously) resulted in little increase in urinary phosphorus although two patients responded to high repeated intramuscular doses After dihydrotachysterol calcium and phosphorus excretion increased and serum values returned to normal

The Ellsworth Howard test gave misleading results In the three cases the condition would have been diagnosed as pseudohypoparathyroidism on the basis of this test when actually it was idiopathic hypoparathyroidism

Pseudohypoparathyroidism Description of Three Cases and Critical Appraisal of Earlier Accounts of the Disease are presented by M E MacGregor and T P Whitehead[4] Certain criteria have been set up for diagnosis Typical physical features are round face short stature and stocky build but it is unwise to seek conclusive support for a diagnosis in body build Mental capacity is also a poor means of diagnostic differentiation between pseudo and spontaneous hypoparathyroidism because examples of backwardness in young persons with spontaneous hypoparathyroidism are known Family history is an imperfect criterion

A test trial with parathyroid hormone intramuscularly should be made A normal person responds to moderate doses with a slight but definite rise of serum calcium level Hypoparathyroid patients react to smaller doses with a greater rise Patients with pseudohypoparathyroidism have no reaction though there are other reasons for lack of response e g severe tetany after removal of parathyroid adenoma or steatorrhea with tetany When chondrodys-

(4) A ch Dis. Ch ldhood 29 398-418 October 1954

trophy mainly involving metacarpal and metatarsal bones or ectopic calcification (criteria advanced by Elrick *et al*) has been observed the case has conformed in other ways to the type described by Albright No instance of a satisfactory reaction to parathyroid hormone can be found among such cases In collecting cases of pseudohypoparathyroidism from the literature the authors have considered chronic tetany with brachydactylia and the characteristic metacarpal or metatarsal radiologic changes or with ectopic calcification or bone formation indisputable proof of the condition Low serum calcium and high serum phosphorus levels are found

The Ellsworth Howard test which measures the power of an intravenous dose of parathyroid hormone to increase renal clearance of phosphorus was originally reported to produce in normal subjects a two or threefold increase in phosphorus excretion with or without diuresis Patients with spontaneous or postoperative hypoparathyroidism showed a phosphorus clearance of 10 or more times the resting level Albright and his colleagues confirmed Ellsworth and Howard s results in normal persons but different results were seen in patients with pseudohypoparathyroidism Some had no response others a reduced sensitivity Several recent accounts reveal difficulty in reproducing the earlier results in normal subjects despite the effectiveness of the parathyroid preparation in raising the calcium levels in surgical hypoparathyroidism

Commercial parathyroid extract is assayed biologically on its power to raise the serum calcium level in dogs The method would be satisfactory if the physiologic action of the hormone increased serum calcium and phosphorus levels by its stimulating action on osteoclasts This would result in a raised calcium phosphorus product which returns to normal via enhanced phosphorus excretion Accordingly increase in urinary phosphorus is dependent on raised serum calcium levels If the hormone directly stimulates the kidney to excrete phosphate and the rise in serum calcium is secondary to a consequent fall in serum phosphorus it would imply that the parathyroid hormone recently used in Britain was of low potency but this product can raise serum calcium levels The only satisfactory explanation

found in recent work is that there are two active hormones in the extracts

The explanation of the difference in response to parathyroid hormone found by Albright and that found by more recent British investigators therefore may be that over a period of years changes have been made in the manufacture of the extract which have not affected its power to raise serum calcium levels but have altered its power to increase urinary phosphorus excretion If the parathyroid gland excretes two hormones and the authors believe there is strong evidence for this there would have to be two simultaneous target organ defects' in pseudohypoparathyroidism if Albright s target organ defect hypothesis is accepted The defect if it exists must be incomplete at one end organ because parathyroid extract is sometimes able to provoke a rise in serum calcium in pseudohypoparathyroidism Some explanation other than end organ insensitivity is required for the puzzling responses in these cases particularly because cases of steatorrhea with tetany have been encountered with precisely similar aberrations in response

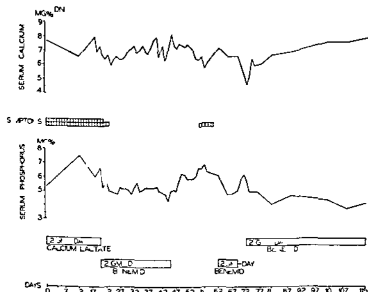
Influence of Benemid® on Urinary Excretion of Phosphate in Hypoparathyroidism is described by Luke R Pascale Alvin Dubin and William S Hoffman (Cook County Hosp) Five patients with clinically established hypoparathyroid tetany were maintained on a diet containing 0 5 Gm calcium and 1 2 Gm phosphorus and given 1 Gm benemid® two three or four times daily without ill effects (Fig 113) Within 48 hours after institution of benemid® therapy serum phosphate levels were lowered in all five patients In two quantitative urinary studies showed that the fall in serum phosphate was caused by an increased excretion of the ion When the drug was discontinued the phosphate levels returned to control values Since no phosphaturic effect has been noted in normal or gouty subjects it is clear that any inhibitory effect of benemid® on tubular reabsorption of phosphate is masked by the normal action of the parathyroid hormone

With the fall in serum phosphate levels tetanic symptoms became milder or ceased This usually occurred without any increase in the serum calcium level but when

(5) Metabol m 3 462-470 September 1954

large quantities of calcium were available in the diet the serum calcium level rose slowly though it never reached normal limits It was postulated that this effect was due to increase in the serum calcium ion concentration even though the total calcium level remained unaltered

Clinically the value of benemid® in prolonged treatment of chronic tetany appeared limited It was less reliable and



F g 113—C rv h w g h ng in s rum l m d ph phoru lev ls w th ben m d® th py in p t t w th h pop thy d tet y (C rt y f P s- l L R t l M t bol m 3 46 -470 S pt mb 1954)

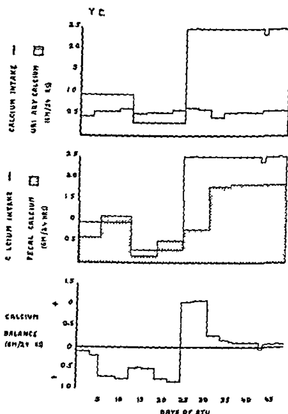
less effective than dihydrotachysterol and the large dose required might have become harmful if continued for a long period

[This and the preceding article demonstrate the difficulty of proving the diagnosis of pseudohypoparathyroidism. Although a normal response to the Ellsworth Howard test eliminates this disease an abnormal result is not definite proof that the patient is unresponsive to parathyroid hormone In such cases a prolonged trial of the hormone with balance studies is necessary—Ed.]

Effect of Diet on Metabolic Alterations of Paraplegia
D M Wyse and C J Pattee[6] (Montreal) conducted cal

(6) Ca d. M A J 71 235 238 S ptembe 1954

cium and phosphorus balance studies in two paraplegic pa tients One man 24 had traumatic flaccid paraplegia of 40 days duration the other 26 had had traumatic paraplegia for 2½ months The study was divided into three periods



F g 114 —Effect of l w a d h gh c lc um tak s on u mary a d fec l alcium le els a d c lc balan n p t e t aged 26 (Court sy of Wy e D M and P ttee C J Canad M A J 71 235 238 Sept mber 1954)

of 12 days each a control period a low calcium low phos phorus period and a high calcium high phosphorus period Urinary calcium excretion during the control period was considerably higher than normal in both patients and con tinued high during the low calcium low phosphorus intake With high calcium intakes one patient s calcium excretion increased and the other s remained unaltered There was a

close relationship between calcium intake and fecal calcium The calcium balance study indicated a negative balance in one patient during both the control period and the period of low calcium intake but a positive balance throughout the

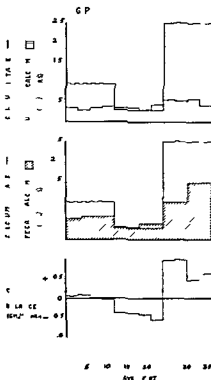


Fig 115.—Effect of low and high calcium intakes on urinary and fecal calcium levels and calcium balance ... (Courtesy of Wyse D M and P ... C J Canad. M A. J 71 235 ... September 1954)

period of high intake (Fig 114) The other patient was in calcium equilibrium during the control period in negative balance during low calcium intake and in positive calcium balance during high calcium intake (Fig 115)

A low calcium intake did not lower the hypercalcinuria already present and affected the calcium balance adversely

High calcium intake appeared to induce positive balance or equilibrium

It was concluded that a high calcium low phosphorus diet might be the diet of choice in paraplegia with calcium given as lactate Urinary calcium should be checked before and soon after institution of such a diet to make sure that no significant rise in calcium excretion occurs

[The combination of osteoporosis and renal calculi complicates therapy in a variety of paralytic diseases These studies suggest that dietary calcium restriction does not protect the kidneys and may accelerate the skeletal damage —Ed]

NUTRITION AND BODY COMPOSITION

Body Sodium and Potassium III Inter related Trends in Alimentary Renal and Cardiovascular Disease, Lack of Correlation between Body Stores and Plasma Concentration Francis D Moore Isidore S Edelman John M Olney Anthony H James Laura Brooks and Graham M Wilson[7] (Harvard Med School) determined total exchangeable potassium and sodium levels in a variety of pathologic conditions and compared the values with those in healthy adults

In obesity the values for both cations were reduced In chronic disease of the alimentary system leading to body wasting there was a decrease in exchangeable potassium and an increase in exchangeable sodium In renal failure accompanied by elevation in serum potassium concentration exchangeable potassium was reduced In advanced mitral stenosis a slight elevation of total exchangeable sodium with a slight lowering of total exchangeable potassium was seen In severe hypertension exchangeable sodium was within the normal range Variations in blood pressure following adrenalectomy were not accompanied by alterations in exchangeable sodium and no correlation between the two was evident In edema exchangeable sodium was greatly increased and exchangeable potassium reduced

In the entire series there was no definite correlation be

(7) Metabolism 3 334 350 July 1954

tween serum levels and the corresponding measurement of exchangeable sodium and potassium The two varied independently and at times inversely Therefore when depression or elevation of the serum concentration of these ions is observed clinically one must be guarded in concluding that a deficiency or excess is present in the body

Depletion due to a variety of conditions produced a compositional syndrome characterized by (*a*) a high total exchangeable sodium level with a low serum sodium concentration (*b*) a low total exchangeable potassium level with a high serum potassium concentration (*c*) a high water fraction a large proportion of which appeared to be extracellular and (*d*) a low fat fraction

[The lack of correlation between total exchangeable ions in the body and serum ion concentration is certainly important The data in this article, however are expressed in terms of body weight rather than as total quantities This may cause misleading interpretations for example the total body sodium in obesity is higher than normal but increased proportion of fat reduces the relative extracellular fluid volume so that the sod um/kg is low Similar confusion in the opposite direction may also arise in patients with edema It is d fficult to t ll whether the nephritics with high serum potassium concentrations actually have low total body potassium or whether their body weight includes an increased proportion of low potassium extracellular (edema) fluid with a relatively reduced mass of cells which are high in potassium content.—Ed.]

Electrolyte Excretion during Experimental Potassium Depletion in Man B M Evans N C Hughes Jones M D Milne and S Steiner[8] (Postgraduate Med School London) produced potassium depletion in two healthy men by daily administration of a low potas ium diet and 50 Gm sodium sulfonic cation exchange resin Each gram of resin exchanged approximately 0 5 mEq potassium ion for sodium The effect of potassium depletion on the diurnal rhythm of electrolyte excretion was observed during the first six or seven days of depletion and the effect of conditions normally causing increased potassium excretion was studied from the seventh to the ninth day when depletion was maximal

The following stimuli which usually increase potassium excretion were used (1) water diuresis following rapid ingestion of 1 L distilled water (2) osmotic diuresis by rapid intravenous infusion of 300 ml of 25% mannitol in aqueous solution (3) hyperventilation by breathing through a re

(8) Ch Sc 13 305-316 M y 1954

cording spirometer for two hours at 2½ times the basal ventilation rate (4) ingestion of 10 Gm of sodium bicarbonate in aqueous solution (5) ingestion of 250 mg carbonic anhydrase inhibitor 2 acetylamino 1 3 4-thiodiazole 5 sulfonamide (diamox®) and (6) ingestion of 10 Gm potassium chloride in aqueous solution

It was found that following dietary potassium depletion the normal kidney is capable of efficient conservation of potassium despite stimuli which normally result in increased potassium loss i e hyperventilation osmotic diuresis from intravenous mannitol and ingestion of sodium bicarbonate carbonic anhydrase inhibitor and potassium chloride

The results were compatible with the theory of competition between the potassium and hydrogen ion for exchange with sodium in the distal tubules of the kidney but showed no compulsion that this exchange occur when availability of both potassium and hydrogen is reduced During potassium depletion diurnal variation of potassium excretion was diminished while that of other electrolytes remained unchanged supporting the hypothesis that a tubular ionic exchange is important in initiation of this diurnal rhythm A recent claim that citrate excretion is reduced during potassium depletion was not confirmed

Dehydration with Hypernatremia Hyperchloremia and Azotemia Complicating Nasogastric Tube Feeding Frank L Engel and Carl Jaeger[9] (Duke Univ) observed five cases after tube feeding of diets relatively high in protein (125 200 Gm daily) to patients with impaired levels of consciousness The diet was being used routinely without appreciation of increased water requirement imposed by the high protein intake Development of this syndrome generally was associated with deterioration of the clinical condition Except for one patient who died before corrective measures could be taken the hyperosmolarity was restored to or toward normal by reducing protein content of the diet or increasing fluid intake or both Thus the interpretation that the high protein intake was an important if not the chief contributing factor was substantiated

In most cases the possibility of dehydration was obscured because fluid intake seemed adequate by usual stand

(9) Am. J Med 17 196-204 A gu t 1954

ards and urine output was generous The high insensible and extrarenal water loss because of fever was not usually recognized nor in general was it appreciated that the large solute load resulting from high protein intake accentuated renal loss of water The latter in turn was exaggerated by excretion of extra solute due to the negative nitrogen balance of these acutely and chronically ill patients

High solute load is not the only cause of dehydration in unconscious patients An unusual type of dehydration occurs with diabetes insipidus particularly when the condition is unrecognized Hyperosmolarity has also been reported with brain damage and must be attributed to disturbance of some regulatory mechanism for salt and water excretion in the central nervous system In many of these reports evidence that the brain lesion was responsible for the hyperosmolarity was unconvincing because the patients were being tube fed Although the composition of the diets generally was not mentioned it is assumed that often they were high in protein There are instances however in which a central nervous system lesion other than one involving the hypothalamicoposterior hypophysial system may play a role in salt and water regulation and in development of dehydration and hyperosmolarity One such case is described

Diet and Plasma Cholesterol Levels G A Mayer W Ford Connell Margaret S DeWolfe and J M R Beveridge[1] (Queen s Univ Kingston Ont) studied the diet of five apparently healthy male experimental subjects The level of natural cholesterol (animal or vegetable fat) was altered at the expense of primarily carbohydrate foods ingested in amounts sufficient to satisfy the appetite and to maintain as constant a body weight as possible Diet no 1 contained 100 180 mg chole terol daily with 10 9 18 9% of total calories as fat and was eaten for four weeks Diet no 2 eaten for one week contained 900-980 mg cholesterol daily with 10 9 18 9% as fat Diet no 3 with 100 180 mg cholesterol daily and 34-46% as vegetable fat was eaten for one week Diet no 4 eaten for two weeks contained 210-300 mg cholesterol daily and 34-46% as animal fat

The diet low in fat and cholesterol led to a highly sig

(1) Am J Clin. N t ition 2 316-322 Sept.-Oct. 1954

nificant decrease in plasma cholesterol levels, but addition of cholesterol as egg yolk caused no change When the proportion of dietary fat was increased as vegetable fat a significant increase occurred in plasma cholesterol levels which were not further significantly increased by substitution of animal for vegetable fat The results indicate that within the limits of the study dietary cholesterol has no effect on plasma cholesterol levels but alterations in the level of dietary fat whether animal or vegetable lead to parallel changes in plasma cholesterol levels

Effect on Human Serum Lipids of Substituting Plant for Animal Fat in Diet is reported by Edward H Ahrens Jr David H Blankenhorn and Theodore T Tsaltas (Hosp of Rockefeller Inst) In a four month study of six obese patients two of them Negroes plant fat was isocalorically substituted for animal fat The patients were hospitalized on a metabolic floor without restriction of activity and were fed solid foods supplemented by fat and protein rich formulas Weights were held constant During the control period of three to six weeks on animal fat feeding the supplement contained butter salad oil eggs and a blended formula of milk cream and frozen egg yolk During the test period of 10 11 weeks on plant fat feeding the supplement contained milk free oleomargarine salad oil peanut butter avocado pear and a blended formula of milk protein dextrose corn oil and milk free chocolate sirup Total calories and caloric composition of the two supplements were almost identical The animal fat supplement contained 140 Gm animal and 10 Gm plant fat The plant fat supplement contained all plant fat except for traces of animal fat Estimated daily cholesterol intakes in the two periods were 1 800 mg and 23 mg respectively

Total and free cholesterols cholesterol esters phospholipids and neutral fat were measured (Fig 116) After acclimatization the concentrations of the lipid fractions varied significantly only when the dietary fat was changed from one type to the other with little fluctuation from week to week Cholesterol and phospholipid values fell abruptly when plant fat was substituted isocalorically for animal fat rose to original levels when animal fat was fed again and re

(2) Proc Soc Exper Biol & Med 86 872 878 Aug Sept 1954

turned to low level, when plant fat was again fed Free and total cholesterol decreased proportionately when plant replaced animal fat cholesterol decreased more than phospholipids and neutral fat levels remained unchanged

The periods of acclimatization and transition are considered important in preventing false rise in serum lipids

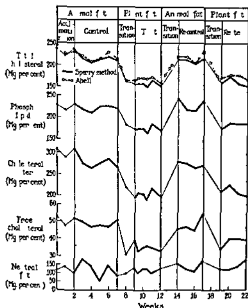


Fig 116—Ch g on t t on f rum l p d wh n m l d pl t f t int k we lte t d oc l cally wh l th di t ry intak em d th m (C rt y f Ah en E H J t l Proc Soc E p B l & M d 86 872 878 A g S pt 1954)

after a person on a fat free diet is fed either animal or plant fat

[The importance of total fat intake in influencing serum cholesterol levels is well illustrated in this and the preceding article The difference between animal and vegetable fat which was demonstrated by Ahrens and his associates have been missed by Mayer s group because the feeding period were too short (1 or 2 weeks compared to 3 10 weeks in the Ahrens study) —Ed]

Clinical Studies in Blood Lipid Metabolism IX Effect of Lipotropic Agents on Serum Lipid Partitions in 50 Patients with Generalized Atherosclerosis Three Year Study

A Allen Goldbloom Harold B Eiber and Linn J Boyd[3] (New York Med College) maintained 50 patients aged 35 75 with generalized atherosclerosis and chronic coronary artery disease on low fat (15 Gm) low cholesterol (100-300 mg) diets for 36 months One half took 9 12 capsules daily of a lipotropic agent each capsule containing 2 5 Gm choline dihydrogen citrate 1 0 Gm dl methionine 0 75 Gm inositol 18 µg vitamin B_{12} and 0 78 Gm liver concentrate

Cholesterol values initially averaged 254 mg/100 cc and after 36 months averaged 224 mg in the controls and 222 mg in the lipotropic group Total lipid levels initially averaged 920 mg/100 cc and after 36 months were the same in both groups Neutral fats originally averaging 430 mg/100 cc fell to identical levels of 372 mg in both groups Phospholipids were identical at the beginning and after 36 months and the ratio of phospholipids to cholesterol was unchanged

Assuming that all 50 patients followed the diet and that 25 of them took the medication the lipotropic substances had no effect against hypercholesteremia, hyperlipemia and lipidosis They had no decholesterolizing action and therefore cannot prevent deposition of lipoid material in the intima or its mobilization from atherosclerotic arteries Low fat low cholesterol diets attained the same end results as lipotropic agents in reducing serum lipid values Loss of weight had no bearing on the diminution of the lipid partitions It is concluded that lipotropic preparations have no value in the treatment or prophylaxis of human atherosclerosis

Blood Lipid Levels as Influenced by Weight Reduction in Women were studied by Norman S Moore Charlotte M Young and Leonard A Maynard[4] (Cornell Univ) Repeated observations of serum lipid levels were made in 24 women aged 16 66 for approximately six months On diets containing about 1 400 calories and 50 80 Gm of fat daily these subjects lost weight at a rate of 0 6-2 lb per week or a total of 16-59 lbs Controls were 12 women aged 13 59, who were not successful in losing weight because of failure to follow the prescribed diet Serial blood samples were analyzed for

(3) Am. J Digest. Di 21 152 157 Jn 1954
(4) Am. J Med. 17 348 354 September 1954

total serum lipids serum phospholipids and serum cholesterol Wide fluctuation in blood lipids was noted in both groups whether they lost weight under dietary control or changed little in weight with no dietary control There was no relationship between level of fat in the diet or percentage of estimated caloric intake derived from fat and changes in the serum lipid levels

The data do not support the concept that weight loss is accompanied by a drop in cholesterol or other blood lipids On the contrary a slight rise was noted in most subjects In the case of serum cholesterol and phospholipids statistical analysis revealed an increase of 0 58 mg cholesterol and 0 64 mg phospholipid per pound of weight loss both were significant at the 5% level

[These observations confirm the statements of Keys (this YEAR BOOK p 406) that plasma lipid patterns are not correlated well with body weight They do not support the observations of Keys Mayer (p 673) and many others that the quantity of fat in the diet is correlated with plasma lipid concentrations —Ed]

Caloric Value of Labile Body Tissue in Obese Subjects five otherwise healthy women was studied by Vincent P Dole Irving L Schwartz Niels A Thorn and Lawrence Silver[5] (Rockefeller Inst) Small changes in body weight were correlated with known variations of caloric intake The ratio of these two quantities—the caloric equivalent of labile body weight—sets an upper limit to the energy value of primary storage tissue The patients physical activity remained nearly constant from day to day They were fed a formula of constant composition in six equal portions during the day The formula consisted of evaporated milk corn oil dextrose and water and contained 1 427 available calories and 21 8 mEq sodium/L The amount given daily was adjusted approximately to maintenance value for each patient During the periods of excess 55 Gm formula was added to each of the six feedings a total of 485 calories daily During the period of deficit 55 Gm was deducted from the baseline amount Changes in body weight correlated with caloric variations were substantially larger than might be expected from variation of dietary sodium The ratio of change in amount of dietary sodium to correlated

(5) J Clin I t 34 590 594 Ap 1 1955

change in body weight was about 37 mEq/kg Therefore even if all the extra sodium were retained and diluted to form extracellular fluid the increment would account for only one fifth of the observed weight gain

The primary reservoirs of energy in these five women had a low caloric value per unit weight probably less than 2 5 calories/Gm This finding was interpreted as evidence that considerable water is stored and released as a part of the fat stores The daily requirement for maintenance on the milk formula was 20 2 24 4 calories/kg

[The relatively high water content of adipose tissue is confirmed by Johnston and Bernstein (J Lab & Clin Med 45 109 January 1955) who used body water dissection technics (see 1954 55 YEAR BOOK pp 664 669) and found that about a third of the adipose tissue was intra or extracellular fluid This would yield a calculated estimate of 6 Cal/Gm of adipose tissue Dole *et al* in measuring primary energy reservoirs was probably including some nonadipose tissue which may account for their lower estimate—Ed]

Comparison between Weight Reduction on High Calorie High Fat Diet and on Isocaloric Regimen High in Carbohydrate was made by Sidney C Werner[6] (Columbia Univ) The high fat diet (Pennington) was calculated from standard tables to provide 2,874 calories/day with 122 Gm protein 242 Gm fat and 52 Gm carbohydrate The baseline high carbohydrate diet was calculated to provide 2 878 calories with 104 Gm protein 146 Gm fat and 287 Gm carbohydrate The patients three males and three females were admitted to the metabolism ward for study Weights were obtained daily before breakfast on a scale accurate to 100 Gm

One patient had a sharp drop in weight on the Pennington diet but had diarrhea Another whose weight dropped while on the high fat diet also lost considerable amounts of sodium One lost slightly in the first week on the high fat diet then slowly gained In two women there was little change in weight on either the baseline or the Pennington diet and the initial and final weights were the same These two who had been amenorrheic for six months before the experiment had menstrual periods on the second day of the Pennington diet (Fig 117) Two males showed straight line weight loss on both baseline and Pennington diets

A high fat low carbohydrate diet and an isocaloric diet

(6) New England J Med 252 661 665 Apr 21 1955

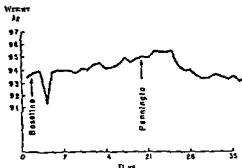


Fig 117 —W ght rv f wom 26 h wt g w ght se d bsequent f B P t ent men t u ted econd day f P nn gton g m (C rt y f W rn S C New E gla d J Med 25 661 665 Apr 21 1955)

high in carbohydrate and low in fat are handled similarly by the body in terms of response of body weight No difference in weight loss between the two diets was observed in two males and slight differences in weight los between the diets noted in three women and one man were due to salt and water variations

Ketone Metabolism in Obesity II Aage Warming Larsen[7] (Copenhagen) studied the degree of inanition ketosis in 42 obese and 25 normal persons All were confined to bed for one or more fasting periods of three days each after receiving a standard diet for three days before the starvation In 24 patients the starvation periods were repeated after a week on low calorie diets In the obese and normal subjects blood ketone level at the beginning of the fasting period were the same and in both groups the levels gradually increased during the three days of starvation then remained constant

The levels of ketones in the blood on the morning of the fourth day of starvation were compared Of the 25 controls 18 had concentrations between 11 and 30 mg 2 had less than 10 mg and 5 had over 30 mg /100 cc of beta hydroxybutyric acid Of the 42 obese patients 12 had ketone concentrations between 11 and 30 mg 12 had less than 10 mg and 15 had more than 30 mg /100 cc of beta hydroxy butyric acid Low calorie diets for a week before the star

(7) Acta med sc d 150 475 1954

change in body weight was about 37 mEq/kg Therefore even if all the extra sodium were retained and diluted to form extracellular fluid the increment would account for only one fifth of the observed weight gain

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A high fat low carbohydrate diet and an isocaloric diet

(6) New England J Med 5 661 665 Apr 21 1955

established urinary uric acid output reaching approximately normal values Probably uric acid in the solid phase is in equilibrium with that in body fluids

Since no consistent relationship can be established between uric acid levels and acute gout a precursor of uric acid and not uric acid itself may be responsible for the acute paroxysm There are few data on which to decide whether the precursor is normal or abnormal but if colchicine acts by blocking its formation the precursor must be abnormal since the colchicine has no effect on plasma uric acid level In the gouty patient metabolism of glycine to uric acid may be via an abnormal route This hypothesis is consistent with the occurrence of acute attacks of gout after probenecid administration had produced uric acid diuresis and brought the blood level of uric acid to normal for it is possible that by removing the end product of the metabolic chain the formation of precursors might even be increased

Prevention and Treatment of Chronic Gouty Arthritis Alexander B Gutman and T F Yu[9] (New York) described results obtained with combined uricosuric drugs and dietary regulation in chronic gouty arthritis Therapy is indicated whenever there is visual or roentgenographic evidence of tophi or of persistent gouty joint swelling or stiffness encountered in about half the patients with gout The essential aim of therapy is to induce and maintain a negative uric acid balance The effectiveness of dietary restriction is limited since uric acid is derived from simple nitrogen and carbon precursors in the catabolism of protein fat and carbohydrate Uric acid production continues on any dietary and even in the fasting state In some patients a low purine and fat intake and a moderate protein intake are essential for the maximal uricosuric effect

The basic diet used by the authors is low in purines poor in fat and contains 60 70 Gm protein daily derived exclusively from cereals grain products eggs cheese milk nonleguminous vegetables and fruits Most patients are allowed 2-4 oz of meat fish or fowl daily for several days each week Probenecid is given usually beginning with 1 Gm each day and the dose changed as necessary A large

(9) J A M A 157 1096-1102 Mr 26 1955

vation period had no significant effect on ketone levels after starvation

These results are interpreted as probably showing significant variations in starvation ketonemia between obese patients and normal persons On a normal diet the blood ketone concentration is the same in normal and in obese persons and the rapidity with which starvation ketosis reaches a maximum plateau is the same in both groups but ketone concentration after starvation in obese persons shows greater variation than in normal persons

[The dangers of ketosis induced by rapid weight reduction have been discussed by earlier authors (e g Newburgh Arch Int Med 70 1033 1942) Apparently the obese patient is more susceptible to this complication of caloric restriction than is a person of normal weight—Ed]

METABOLIC DISEASES

Studies on Effect of Probenecid (Benemid®) in Gout R M Mason[8] (West London Hosp) gives data on seven cases of gout treated with probenecid in which urinary uric acid and blood uric acid were determined at the same time Four patients had acute attacks and one had an exacerbation of an acute attack when probenecid had reduced the blood uric acid to normal

Total excess of uric acid excreted in the urine was compared with the change in uric acid of the total plasma volume in five cases The calculated loss of uric acid from the plasma was much less than the excess excreted Mean loss of plasma uric acid during five days of probenecid therapy was 149 mg and mean excess of uric acid in the urine 2 136 mg Mean loss of extracellular uric acid was 588 mg Analysis of the total body uric acid revealed a mean loss of 2 173 mg The discrepancy may come from the solid phase of uric acid It is possible that the flow of uric acid from tissue fluids to blood requires some time for equilibrium to develop so that the concentration of uric acid in the plasma does not reflect the concentration in body fluids as a whole

In one patient treated for a long time equilibrium was

(8) A n Rh mat Di 13 120 130 J n 1954

status Serum uric acid level averaged about 11 mg 14 months after the uricosuric drugs were discontinued but the patient was asymptomatic without visible recurrence of tophi

CASE 2—Man 82 had progressive disability and deformity due to chronic gouty arthritis with a steady increase in size and number of tophaceous deposits over many years Serum uric acid level was 8 1 mg/100 ml Probenecid 1 Gm daily and a low purine low fat diet were started Intake of meat fish or fowl was reduced to medium portions every day but further restriction was not accepted by the patient Serum uric acid level fell to 6 6 5 mg and after probenecid was increased to 1 5 Gm daily was maintained at 5 mg After nine months of therapy there was a progressive decrease in the tophaceous deposits on the feet and later on the hands (Figs 118 and 119) He almost completely recovered use of his hands No new tophi have appeared

[The importance of a low purine diet is debatable (viz Case 2) The institution of Gutman s reg men does not produce immediate re ults and the patient should be forewarne l that he may even have acute gouty at tacks while being treated. The e attacks should not interrupt the general plan of therapy but may be handled by the addition of colchicine as in Case 1—Ed]

Porphyria Clinical and Neuropathologic Report Gabriel A Schwarz and James A L Moulton[1] (Univ of Pennsylvania) report clinical and laboratory findings in three fatal cases of acute intermittent porphyria

Girl 17 had had recurrent abdominal pain for a year with dysuria and vomiting Urine was red brown blood pressure 145/105 white blood cell count 13 550 and sedimentation rate elevated Appendectomy revealed a hyperemic appendix Postoperatively she complained of numerous aches and pains blurred vision and diplopia Behavior was erratic and confused and she became stuporous comatose hallucinated and progressively weaker Urine contained urobilinogen and uroporphyrin She died 19 days after operation At autopsy neuropathologic studies revealed acute toxic changes in the neurons of the cortex with fragmentation paling and dispersal of Nissl substance and swelling of the cell bodies Blood vessels in the meninges of the spinal cord and spinal nerve roots were dilated and engorged In the substance of the spinal cord were engorged and dilated blood vessels and occasional fresh perivascular hemorrhages There was some decrease in number of anterior horn cells Some remaining anterior horn cell were well preserved but most of them stained darkly with loss of distinct Nissl granules and nuclei and attenuation of many of their processes (Fig 120)

Neuropathologic studies in another case showed changes in the leptomeninges intrinsic vascular structure of the neuraxis and neurons of the autonomic ganglions and central nervous system These changes are probably best ex

(1) A M A A h I t M d 94 221 247 A g t 1954

fluid intake is advised and occasionally alkalinizing agents are recommended to avoid precipitation of uric acid in the urinary tract

In most of 30 patients with disability due to chronic gouty arthritis observed for eight months to four years it was possible to alleviate pain and stiffness of joints and reduce the size of tophaceous deposits No new tophi developed while treatment was adequately maintained

CASE 1 —*Man 66 over 18 years had many attacks of acute gouty* arthritis with progressively larger and more numerous tophaceous



Fig 118 (left) —Appearance of hand shortly after therapy was begun
Fig 119 (right) —After about two years of therapy
(Courtesy of Gutman A B and Yu T F J A M A 157 1096-110 M 26 1955)

deposits Serum uric acid level was consistently above 11 mg /100 ml and mean urinary uric acid excretion was 500 mg /24 hours Prophylactic doses of colchicine 1 mg daily a low purine low fat diet and 2 Gm probenecid daily were given Serum uric acid decreased and uricosuria increased Because of persistent joint pathology salicylates and sodium bicarbonate were added to the regimen Uric acid excretion rose to 700 1 000 mg daily and serum uric acid decreased to 3 3 5 5 mg Diffuse joint pain and stiffness improved with progressive diminution in the tophaceous deposits No new tophi appeared Prophylactic doses of colchicine were continued After 14 months of salicylate therapy he began to show signs of irritability and mental deterioration with increasing memory defects confusion and paranoid delusions Within a week after the salicylate bicarbonate medication was discontinued there was striking improvement in mental state Within a month after salicylate therapy was resumed mental symptoms recurred Uricosuric medication was discontinued again with prompt improvement in mental

Walter T Zimdahl Irving Hyman and Walter F Stafford[2] (Univ of Buffalo) Hepatolenticular degeneration (Wilson s disease) is associated with certain abnormalities which include a high excretion of copper increased absorption of copper through the gut aminoaciduria low coeruloplasmin level increase in copper content of both brain and liver low serum copper level and varying degrees of liver dysfunction The three patients who comprised this series were from a single family and had the chronic pseudosclerotic type of hepatolenticular degeneration with a history of tremor in the upper limbs and dysarthria progressing to titubation of the head and trunk and dystonic rigidity Age of onset varied from 17 to 29 years and the illness ran a course of 5 14 and 15 years In two cases the serum copper level was low and in the third it was within normal limits

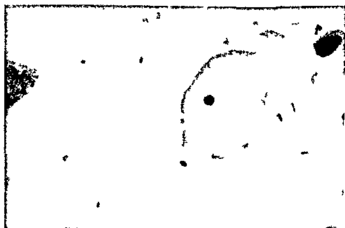
The effect of BAL (2 3 dimercaptopropanol) versene (disodium calcium ethylene diamine tetra acetate) ion exchange resins and ACTH on the copper metabolism of these patients was then studied With administration of BAL tissue copper was mobilized and excreted in large amounts All patients showed clinical improvement although there was little change in liver function Toxic reactions such as transient nausea dizziness occasional vomiting and blurring of vision were encountered Intravenous injection of versene produced an increase in total copper excretion in two patients with Wilson s disease However neither oral nor intravenous administration of this drug in the dosage used produced a negative copper balance Cation exchange resins produced a definite increase in stool copper A negative balance of copper was obtained in two patients on a normal diet however a positive balance occurred on a high copper intake When resin was administered over long periods refractoriness developed but after treatment was discontinued for one to two weeks response was again obtained ACTH produced a transient negative balance of copper in one patient During the course of therapy however this patient s tremor became much worse and his general appearance deteriorated

Because of a significant increase of copper absorption through the gut in Wilson s disease it is recommended that

(2) J Lab & Cl Med 43 774 783 M y 1954

plained as a diffuse toxic reaction—meningopolioenceph alomyelitis

In contrast to these findings the literature discloses that some patients with acute porphyria presented severe neu rologic signs and symptoms without abnormal neuropatho-logic changes The lack of findings may have been due to



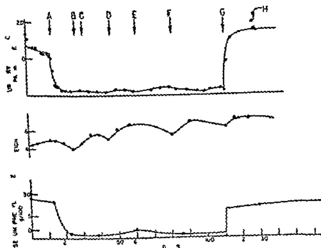
F g 120 —Cerv cal port on f sp nal cord The anter or horn c ll sh ws i tense well ng of t body N l bod es d t y d th gh a few gra l rema at the ll p r phe y a d th l sh u ken d fo m d a d d pl d T l d n blue ×512 (Courtesy of Schwa G A and M ult n J A L A M A A h I t Med 94 1 247 A gu t 1954)

rapidity of the disease process However ultraviolet micros copy has revealed fluorescence of the liver kidneys and costal cartilage and fluorescent droplets scattered through out the spinal cord cerebellar and cerebral cortices and pituitary gland so the effect in cases without anatomic ab normalities may have been at a biochemical level

[The unfortunate sequelae of trauma (including surgery) in unrec ognized porphyria have been emphasized repeatedly in the past. This patient also received barbiturate sedatives postoperatively up to the time of death The cause of porphyria and of the nervous system symptoms is still obscure but the pathologic findings described here suggest that actual anatomic damage to the neurons can be produced and since fluorescent material is seen in the area of the lesions it seems possible that porphy rins (which fluoresce intensely) may have accumulated in the diseased area and produced the lesions by their presence —Ed.]

Effect of Drugs on Copper Metabolism in Hepatolenticu lar Degeneration and in Normal Subjects is described by

After he had returned to a normal diet for four weeks his scalp hair was lighter than on the phenylalanine deficient diet Seizures did not recur although the ECG showed seizure activity of moderate severity 20 months after the special diet was discontinued He became less responsive but still pulled himself to a sitting position



F g 121 —Fxpe m ntal d t ph ylk t A ph yl l n n -d fi ent d t t d B 200 mg l ph yl l d ly C 250 mg D 300 mg E 200 mg F 250 mg G 2 5 Gm d ly H t ral d t (C t f A m t g M D nd Tyl F H J Cl I t 34 565 580 Ap l, 1955)

Effects of a detrimental substance on the central nervous system were overcome by use of the phenylalanine restricted diet Probably such diets should be initiated at an early age to prevent irreversible damage to the central nervous system

patients be placed on a low copper diet plus interrupted resin therapy between periods of treatment with BAL or versene

Studies on *Phenylketonuria* I *Restricted Phenylalanine Intake in Phenylketonuria* Synthetic diets deficient in phenylalanine were given to five children with phenylketonuria by Marvin D Armstrong and Frank H Tyler[3] (Univ of Utah) Blood phenylalanine levels were lowered to normal value phenylpyruvic acid excretion and abnormally high excretion of other metabolites ceased Synthetic diets in which the protein portion was composed of pure amino acids were used There was improvement in behavior in all the children epileptic seizures ceased and neurologic disturbances were decreased while the diet was given

Boy 4 with extreme mental retardation was thought normal until age 5 months He had severe otitis media and repair of umbilical hernia at that time Recurrent eczema was a problem At 7 months *he had seizures which became progressively more severe uncon*trolled by heavy sedation He led a vegetative existence scarcely responded and had not learned to sit or play He had two siblings with phenylketonuria three paternal great aunts with convulsive disorders who had died in infancy and three collaterals of the maternal great grandmother who were mentally retarded or had had seizures Neurologic examination revealed increased muscular tone with cog wheel rigidity of the arms and legs Intermittently he developed opisthotonos with irregular clonic movements of arms and blinking of eyes Between episodes he chewed on his arms When frightened he abruptly stiffened had tremors of the extremities and skin showed large blotchy red areas He had no dermatitis The fasting serum phenylalanine level was *42 mg/100 ml* and addition of ferric chloride to the acidified urine produced a deep greenish black color The ECG disclosed abnormal activity with bursts of diffuse slow waves and periods of petit mal variant activity most prominent over the occipital lobes

On the experimental *diet he gradually gained weight Increase in* blood phenylalanine levels was noted on adding *300 mg* phenylalanine to his diet daily *200 mg* daily allowed the level to decrease (Fig 121) Seizures disappeared without sedation he learned to sit up and eventually pulled himself to a sitting position He became responsive and played with toys There was some decrease in spasticity and the cog *wheel rigidity disappeared The marked stiffening* and tremors and the discolored patches of skin were no longer apparent when he was frightened The seizure pattern disappeared from the ECG

(3) J Cl In st. 34 565 580 April 1955

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